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ORIGINAL ARTICLE

Oral tranexamic acid with a triple combination cream versus oral tranexamic acid monotherapy in the treatment of severe melasma

Jessica Carolina Martinez-Rico MD | Sonia Chavez-Alvarez MD | Maira Elizabeth Herz-Ruelas MD, PhD | Sergio Axel Sosa-Colunga MD | Jorge Ocampo-Candiani MD, PhD | Yeudiel Suro-Santos MD | Osvaldo Vazquez Martinez MD, PhD

Department of Dermatology, University Hospital "Dr. Jose Eleuterio Gonzalez", Universidad Autonoma de Nuevo Leon, Monterrey, Mexico

Correspondence
Vazquez Martinez Osvaldo, Dermatology Department, Facultad de Medicina, "Dr. José E. González" University Hospital, Universidad Autónoma de Nuevo León Francisco I. Madero y Av. Gonzalitos s/n, Mitras Centro, Monterrey, Nuevo León, México.
Email: vazquez_osvaldo@hotmail.com

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Abstract

Background: Melasma is an acquired pigmentation disorder with a complex multifactorial etiopathogenesis. Oral tranexamic acid (TA) is a promising drug for its treatment and may enhance outcomes when used in combination.

Objective: To provide evidence of the efficacy and safety of oral TA as a monotherapy, and in combination with a triple combination cream, for treating melasma in the Hispanic population.

Methods: Forty-four female Hispanic patients with melasma were randomly assigned to receive 325 mg of oral TA every 12 h plus f-TCC (fluocinolone-based triple combination cream) every 24 h (group A) or 325 mg of oral TA every 12 h (group B) for 8 weeks, after which both groups were crossed-over, and treated for an additional 8 weeks. Evaluations of the mMASI score, the melanin index, and the MelasQoL were made at baseline and Weeks 4, 8, 12, and 16.

Results: There was a 50.04% and 65.45% improvement in mMASI at Weeks 4 and 8, respectively, in group A, compared to baseline, while for Week 16, an improvement of 76.85% was achieved in group B compared to baseline. Highest scores were consistent with the use of the combined treatment modality in both groups, and were evidenced by the values of the melanin index obtained. There was no significant difference in MelasQoL scores between the 2 groups. No serious side effects were observed.

Conclusion: The combination of oral TA and f-TCC is more effective than oral TA alone in the treatment of severe melasma in Hispanic patients.

KEYWORDS
Hispanic patients, melasma, oral tranexamic acid, pigmentary disorders, triple formula

1 | INTRODUCTION

Melasma is an acquired centrofacial pigmentation disorder that occurs mostly in women with high skin phototypes. Its prevalence ranges from 8.8% in Hispanic populations to 40% in Asian populations.[1] It is known to cause significant impairment to the patient's quality of life, and available treatments include topical formulations, chemical peels, lasers, and light devices, with inevitable sunscreen

Correction added on 22 June 2022, after first online publication: The word 'melisma' changed to 'Melasma' in the article title.

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usage, regardless of the choice of treatment. Nevertheless, there is no specific treatment of choice for all cases, and a triple combination cream (hydroquinone, steroids, and tretinoin) represents the most effective initial treatment.[2]

Tranexamic acid (TA) emerged as an alternative treatment for melasma since 1979.[3] It elicits its action by inhibiting the plasminogen activator (PA); thereby, inhibiting the conversion of plasminogen to plasmin in epidermal cells, which is otherwise induced by exposure to ultraviolet (UV) rays. This suppresses the activation of melanogenesis by the blockage of prostaglandin and leukotriene secretion through this keratinocyte-PA UV-dependent system.[4]

Oral TA treatments seem to provide better outcomes than topical and intradermal TA treatments, which have also been used.[5] Despite the increasing popularity and promising outcomes of treatment with TA, recent reviews have indicated that randomized clinical trials from centers outside of Asia are needed to document the efficacy and safety of oral TA alone or in combination with other topical drugs in non-Asian populations.[6,7] The goal of this study was to provide evidence regarding the safety and efficacy of TA as a monotherapy and in combination with a fluocinolone triple combination cream (f-TCC) in the Hispanic population.

2 | MATERIALS AND METHODS

2.1 | Study design

This study, carried out from April 2019 to July 2020, was approved by a review board in a tertiary center in Mexico, and all patients provided written informed consent.

Included in this study were Hispanic women aged 18–50 years, of Fitzpatrick phototypes III - V, with severe facial melasma, defined by a modified Melasma Area and Severity Index (mMASI) score ≥8 based on previously established parameters.[8]

We excluded pregnant or breastfeeding women, active smokers or those who quit smoking within 3 months of the start of study, patients with additional pigmentary disorders, kidney diseases, endocrine disorders associated with hyperpigmentation, family or personal history of thrombosis or hypercoagulability disorders, those who were on hormonal treatments such as hormonal contraceptives or hormone replacement therapy, those who had unrealistic expectations, and/or those who had received treatment within 3 months prior to the study.

The patients were randomized by coin tossing in order of arrival, to receive for 8 weeks either 325 mg of oral TA every 12 h plus f-TCC (fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%) every 24 h (group A) or 325 mg of oral TA every 12 h (group B).

After the first 8 weeks of treatment, both groups were crossed-over, in such a way that patients in group A received only 325 mg of oral TA every 12 hours, and patients in group B received 325 mg of oral TA every 12 hours plus f-TCC every 24 hours for an additional 8 weeks. The dosage of TA was established based on a presentation available in Mexico. Both groups were instructed to apply sunscreen with SPF 50 (Cetaphil Sun®) every 3 h.

Patients were evaluated at Weeks 0, 4, 8, 12, and 16. Demographic data were collected at baseline and at each visit; mMASI was calculated by two blinded experienced dermatologists; objective analysis was carried out by calculating the melanin index using the Mexameter® (Courage-Khazaka Electronic) system; a narrow-band reflectance spectrophotometer, the working principle of which, is based on the absorption/reflection of light by the skin, was used for the evaluation of the melanin index. Reduction in melasma pigment was revealed by a decrease in the melanin index, which is scored from 0 to 1000, with 0 and 1000 representing white and completely black, respectively. We analyzed the same spot each visit in every patient, and the melanin index obtained were compared from the baseline vs every visit (Weeks 4, 8, 12, and 16). In addition, iconographies were taken, and a validated melasma quality of life questionnaire (MelasQoL) was applied.[9]

2.2 | Statistical analysis

The collected data were entered into a Microsoft excel database for subsequent analysis using the R v4.0.3 statistical software. Traditional descriptive statistics (measures of central tendency, dispersion, and position) were used to express quantitative variables, while qualitative variables were expressed as frequencies. The variables were segmented according to the evaluation time and the group to which it was randomly assigned, and contrasted using the Student's *t*-test for the means obtained for quantitative type variables, and the Z-test for proportions. The reliability level was set at 95%.

3 | RESULTS

Of 124 patients evaluated, 52 met the inclusion/exclusion criteria, and 44 agreed to participate in the study. They were randomly assigned to groups A ($n = 22$) or B ($n = 22$) (Figure 1). Patients' characteristics are summarized in Table 1.

Of the 44 patients included 43 completed the study, as one participant was not present for the last evaluation.

A family history of melasma in first-degree relatives was observed in 56.8% ($n = 25$) of the participants.

Forty-one participants were of reproductive age, while 3 were at menopause.

Of these participants, 2 (4.5%), 15 (34.1%), 23 (52.3%), and 4 (9.1%) had phototypes II, III, IV, and V, respectively.

Regarding topography, 75% ($n = 33$) of the patients had a centrofacial melasma pattern, 20.5% ($n = 9$) had malar melasma, 4.5% ($n = 2$) had mandibular melasma, and 9.1% ($n = 4$) also had extra facial melasma in the V region of the neckline.

All patients ($n = 44$) reported the existence of a trigger, the most prevalent being intense sun exposure (81.8%, $n = 36$), followed by pregnancy (34%, $n = 15$), topical treatments (13.6%, $n = 6$), hormonal contraceptives (11.3%, $n = 5$), hormonal treatments (6.8%, $n = 3$), and physical cosmetic procedures (chemical peel) (2.2%, $n = 1$).

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FIGURE 1 Flow diagram

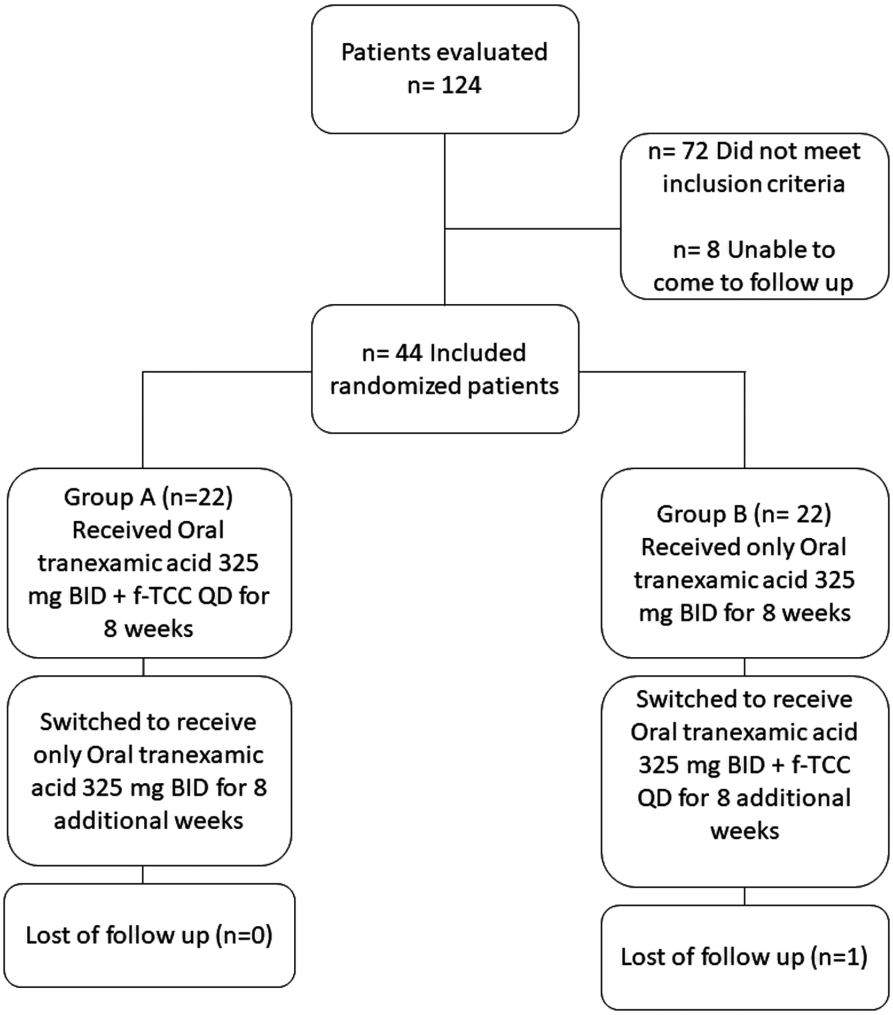


TABLE 1 Patient characteristics at the beginning of the study

	Group A			Group B			
	N	Mean	SD	*N*	Mean	SD	*p*-Value
Age	22	40.45	3.88	22	42.82	4.90	0.0826
Age of melasma onset	22	30.36	5.93	22	33.36	6.11	0.1059
Age at dx	22	37.36	6.46	22	39.36	5.90	0.2897
Time of evolution (years)	22	9.73	6.12	22	9.50	6.53	0.9046

Abbreviations: dx, diagnosis; SD, standard deviation.

The mMASI evaluation in group A showed an improvement of 50.04% and 65.45% at Weeks 4 and 8, respectively, compared to baseline; however, at Weeks 12 and 16, this percentage slightly decreased to 49.18% and 35.31%, respectively.

In group B, an improvement of 42.22% and 60.74% was observed at Weeks 4 and 8, respectively, compared to baseline; at Week 16, a statistically significant ($p = 0.001$) improvement of 76.85% was observed compared to baseline (Table 2, Figure 2). The combined treatment modality gave the highest percentages in both groups.

A marked decrease in melanin index was observed at Weeks 4 and 8 in group A compared to group B, and this was statistically significant ($p = 0.026$ 0.016, respectively). At Week 16, the melanin index was lower in group B than in group A ($p = 0.035$), and the most significant decrease in score was observed with the combined treatment modality in both groups (Figures 3 and 4).

There was no significant difference in MelasQoL scores between the 2 groups. All patients seemed to have an improved quality of life after both treatments (Table 2).

The observed side effects were mild and did not require discontinuation of any of the treatments (Table 3). No serious adverse effects were observed.

4 | DISCUSSION

Melasma is a recalcitrant hyperpigmentation disorder that affects millions of people worldwide.[1] However, its pathogenesis is not fully

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TABLE 2 Items evaluated at each visit

	Group A				Group B				*p*-Value mMASI	*p*-Value MelasQoL	*p*-Value MI
	N	mMASI	MelasQoL	MI	*N*	mMASI	MelasQoL	MI			
Week 0	22	10.45	48.86	355.8932	22	10.80	42.86	369.9691	0.386	0.207	0.581
Week 4	22	5.22	38.95	274.7418	22	6.24	38.14	327.8323	0.185	0.880	**0.026**
Week 8	22	3.61	31.14	255.9855	22	4.24	30.59	313.4241	0.414	0.917	**0.016**
Week 12	22	5.31	24.91	276.2573	22	4.42	23.59	279.4700	0.263	0.780	0.884
Week 16	22	6.76	21.45	283.3027	21	2.50	16.67	241.0633	**0.001**	0.242	**0.035**

Abbreviations: MelasQoL, melasma quality of life; MI, melanin index; mMASI, melasma area and severity index

In group B, at Week 16, a statistically significant ($p = 0.001$) improvement was observed compared to baseline in the mMASI score.

In group A, a decrease in melanin index was observed at Weeks 4 and 8 compared to group B ($p = 0.026$, 0.016).

In group B, a decrease in melanin index was observed at Week 16, compared to group A ($p = 0.035$).

understood. Well-known triggers and exacerbation factors include intense UV light exposure, hormonal factors, and family history. Recently, it has been found that melasma is associated with an increase in solar elastosis, increase in number of mast cells, increased vascularization, and disruption of the plasma membrane, with a consequent increase in pendulous melanocytes. Therefore, in addition to being a melanocyte disorder, melasma is also a photoaging associated condition.[10]

Its complex multifactorial etiopathogenesis has led to the development of a wide variety of therapeutic alternatives.

Tranexamic acid is a fibrinolytic agent that has emerged as a promising drug for the treatment of melasma, as it suppresses melanocyte stimulation by inhibiting the release of arachidonic acid products through the blockage of the keratinocyte-PA UV-dependent system, and by decreasing mast cells and angiogenesis.[11,12]

Tranexamic acid dosages reported in previous studies ranged from 500 to 1,500 mg daily, with an average dose of 250 mg taken twice daily reported to be safe in patients without contraindications such as renal failure, history of thromboembolic or procoagulant disorders, smoking, and use of hormonal therapy, such as oral contraceptive pills; thus, it is important to take a detailed clinical history in all cases where treatment with TA is being considered. The most common side effects of treatment with TA are usually mild and include headaches, menstrual irregularities, gastrointestinal discomfort, and musculoskeletal pain.[6]

Del Rosario et al.[13] conducted a study in 39 patients with moderate-to-severe melasma who received 250 mg of TA or placebo twice daily for 3 months, and an mMASI score reduction of 49% was observed in the TA group, against 18% in the control group.

In a study by Padhi and Pradan, carried out in India on 40 patients, where one group ($n = 20$) was assigned to receive daily topical treatment with a triple topical formula (fluocinolone acetonide 0.01%; tretinoin 0.05%; and hydroquinone 2%), and the other group ($n = 20$) was assigned to receive 250 mg of oral TA every 12 h plus the triple cream formula for 8 weeks, a statistically significant reduction in pigmentation was observed faster in the combination group.[14]

More recently, Shihab et al.[15] conducted a randomized trial on 50 subjects, in which one group received a 4% hydroquinone cream and oral TA (group A), and the other group received a 4% hydroquinone cream and placebo capsules (group B), for 3 months. There was a 55% reduction in mMASI after 3 months in group A compared to 10.9% in group B. In addition, Arreola Jauregui et al. performed a retrospective analysis of 53 patients enrolled to receive 650 mg of TA ($n = 27$) (group A) or 650 mg of TA +a 4% hydroquinone cream ($n = 26$) (group B) daily, and found a reduction in mMASI of 46% in group A, against 61% in group B, at Week 20.[16]

In our study, more than half of our patients reported a family history of melasma, and all of them were of reproductive age at the time of melasma onset. A trigger was identified in all cases, with the most frequent being intense sun exposure, followed by pregnancy, and the use of contraceptives or hormonal treatments, supporting the notion that UV radiation, and hormonal or genetic stimulation play an important role in pathophysiology of melasma.

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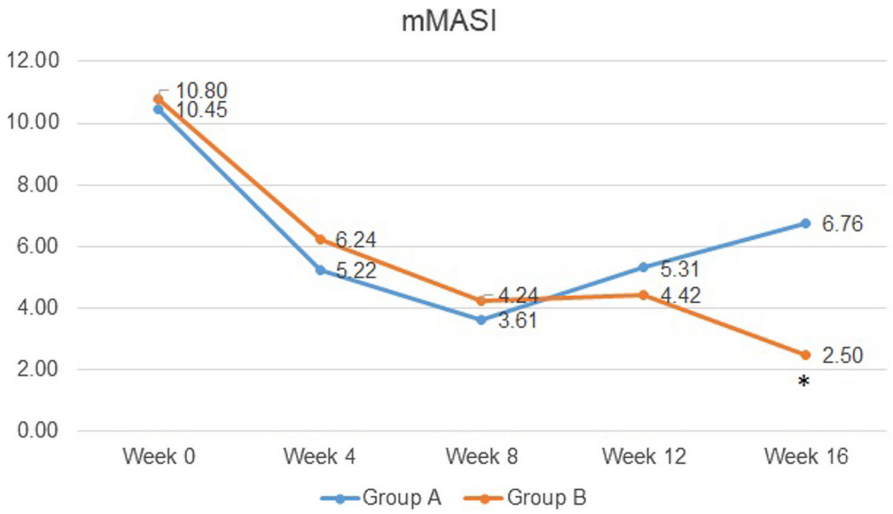


FIGURE 2 Comparison of mMASI scores between Group A and B. *0.001

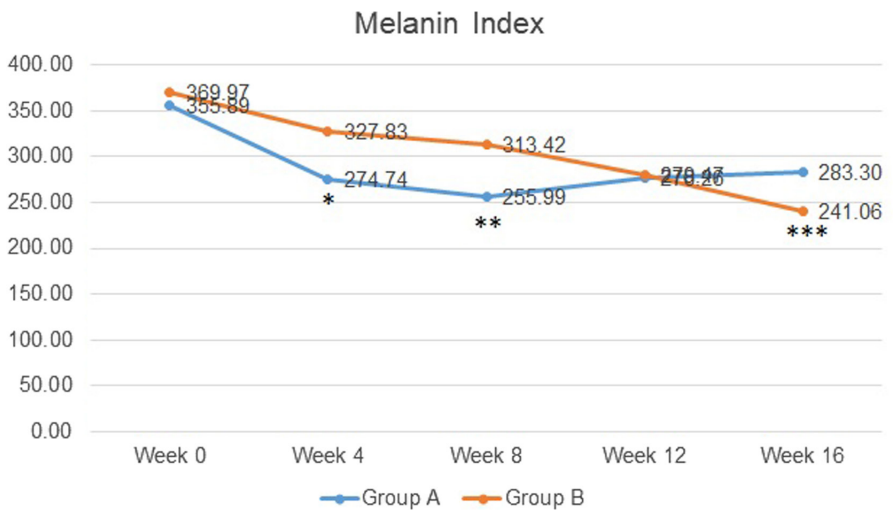


FIGURE 3 Comparison of Melanin indices between Group A and B. *0.026 **0.016 ***0.035

Centrofacial melasma was the most prevalent type of melasma in our patients, as previously reported.[1] The skin phototypes were high, with phototype IV being the most frequent, since people with darker phototypes have a higher risk of developing pigmentary disorders.

A reduction in mMASI of 65.45% was observed in group A against 60.74% in group B at Week 8, whereas at Week 16, the reduction in group B (76.85%) was greater than that in group A (35.31%). This was consistent with the use of the combined treatment modality in both groups and was evidenced by the values of the melanin index obtained.

We observed no statistical differences in MelasQoL of both groups, and we hypothesize that patients felt safer and happier while receiving formal treatment under the supervision of a trained specialist. Only mild adverse effects were observed.

Our findings should be interpreted considering the following limitations: Our study was a single-center study, and a placebo cream was not added to the tranexamic acid monotherapy group. In addition, although we found significant differences in the melanin index before and after treatment, adjacent normal skin was not measured with the Mexameter, and therefore, we did not obtain a true melanin index.

Larger multicenter studies in different populations, with extensive follow-up, were the melanin index is correctly evaluated are needed to provide more standardized information on the duration of treatment with TA, its safety, and relapse upon stopping treatment with TA.

5 | CONCLUSIONS

The use of oral TA in the treatment of melasma at a dose of 325 mg bid was safe during the 4-month treatment period. Combined use of oral TA and f-TCC enhanced outcomes in patients with severe melasma. Nevertheless, oral TA alone equally improved the basal parameters of patients, but to a lesser extent than when it was combined with topical treatment. The MelasQoL showed that there was an improvement in the quality of life of patients, irrespective of the treatment received.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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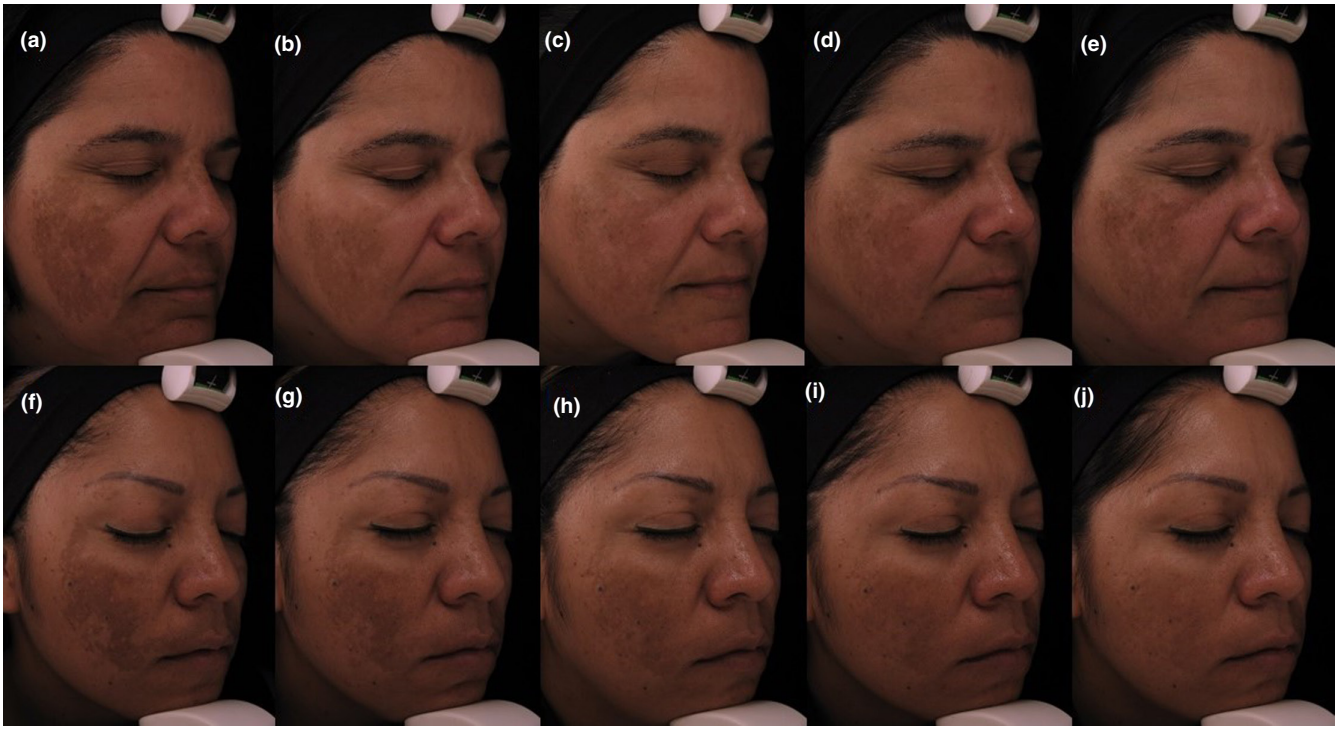


FIGURE 4 Clinical images of patients in group A (A–E), and B (F–J). (A and F) Week 0; (B and G) Week 4; (C and H) Week 8; (D and I) Week 12; (E and J) Week 16

TABLE 3 Adverse events

Adverse event	Oral Tranexamic acid *n* (%)	f-TCC *n* (%)
Oligomenorrhea	7 (15.9%)	0
Gastrointestinal discomfort	2 (4.5%)	0
Burning	0	11(25%)
Erythema	0	8 (18.1%)
Xerosis	0	3 (6.8%)

Abbreviation: f-TCC, fluocinolone triple combination cream.

AUTHOR CONTRIBUTIONS

All authors critically evaluated and approved the final version of the article. Jessica Carolina Martínez-Rico conceived the idea, obtained the measurements, searched and analyzed data, and wrote the manuscript. Chavez-Alvarez Sonia, Herz-Ruelas Maira Elizabeth, Sosa-Colunga Sergio Axel, Ocampo-Candiani Jorge, Suro-Santos Yeudiel, and Vazquez Martinez Osvaldo. helped with data analysis and contributed to the final version of the manuscript.

IRB APPROVAL

Reviewed and approved by local IRB; approval #DE19-00005.

ETHICAL APPROVAL

The study was approved by the local ethics committee (#DE19-00005).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jessica Carolina Martinez-Rico https://orcid.org/0000-0001-7695-8424
Sonia Chavez-Alvarez https://orcid.org/0000-0003-1637-7956
Maira Elizabeth Herz-Ruelas https://orcid.org/0000-0001-6299-1821
Jorge Ocampo-Candiani https://orcid.org/0000-0002-0213-0031
Osvaldo Vazquez Martinez https://orcid.org/0000-0002-3055-2514

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