Received: 13 May 2018 | Revised: 23 October 2018 | Accepted: 31 October 2018

DOI: 10.1111/jocd.12830

ORIGINAL CONTRIBUTION

WILEY JCD Journal of Cosmetic Dermatology

Evaluation of oral tranexamic acid in the treatment of melasma

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Summary

Background: Melasma is an acquired, chronic, recurrent hypermelanosis that occurs exclusively in areas exposed to the sun. Its treatment can be very challenging. Tranexamic acid (TA) is an inhibitor of plasmin, and it is a synthetic derivative of the amino acid lysine that reversibly blocks binding sites on the plasminogen molecule, inhibiting the plasminogen activator from converting plasminogen to plasmin.

Aims: This study evaluated the efficacy of oral TA in the treatment of melasma in patients from a philanthropic dermatological clinic.

Patients/Methods: This was a monocentric, randomized, double-blind, controlled clinical trial. Patients with facial melasma were randomly divided into the following two groups: A (TA 250 mg orally twice daily) or B (oral placebo twice daily). Evaluations were performed before and after 12 weeks of treatment with photographs, colorimetry, MELASQoL, and MASI. All patients were instructed to use tinted sunscreen (SPF 50).

Results: Of the 47 patients selected, 37 completed the study, with 20 in group A and 17 in group B; the patients consisted of one male and 36 females, and the mean age was 43.97 years old. Based on the four methods of evaluation, the melasma in 50% of patients in group A improved versus only 5.9% of patients in group B ($P < 0.005$). There was an improvement according to all evaluation methods in the treatment group. No patient had severe side effects.

Conclusions: We conclude that tranexamic acid was effective in 50% of patients according to four methods of evaluation when compared to the placebo.

KEYWORDS

inhibitor of plasmin, melanin, melasma, oral tranexamic acid

1 | INTRODUCTION

Melasma is an acquired, chronic, recurrent hypermelanosis that occurs exclusively in areas exposed to the sun.[1] This is characterized by brown spots that usually occur on the cheeks, forehead, nose, and supralabial regions.[2] It is a common disorder that occurs in all skin types, all ethnic groups and both genders, but it is relatively more common in darker skin types (phototypes III and IV) and in women of childbearing age.[3-6] Its overall prevalence in the population is 1%.[7]

Melasma pathogenesis has not yet been fully elucidated,[2,8] but exposure to ultraviolet (UV) radiation is considered one of the main causes, in addition to genetic and endocrine factors, drugs, and cosmetics.[3-6]

Family history is also known to be an important risk factor for developing melasma, strengthening the hypothesis of a genetic predisposition to the condition.[9]

The melanogenesis process after exposure to visible UV light can be stimulated by keratinocytes and fibroblasts. One major pathway

of both UV- and visible light-induced pigmentation is the secretion of stem cell factor, the ligand for the tyrosine kinase receptor (c-kit), which leads to downstream effects on the proliferation of melanocytes. It is believed that UV light induces reactive oxygen species (ROS) by activating nitric oxide and promoting melanogenesis.[7]

Other studies found increased vascularity in the affected skin and increased expression of angiogenic factors in the epidermis that may play roles in melasma pathogenesis.[10]

Some histological findings are characteristic of melasma. The amount of melanin is increased in all layers of the epidermis. Melasma is also related to prominent solar elastosis, an increased number of blood vessels and elevated expression of vascular endothelial growth factor (VEGF). An increased number of mast cells in the lesional dermis and increased expression levels of c-kit and stem cell factor have also been reported. Such findings show that several dermal changes, as well as increased epidermal pigmentation, are associated with melasma.[11-16]

As a chronic disease with several contributing factors, the treatment of melasma can be very difficult because the main objective is the improvement of pigmentation and the patient's self-esteem. A number of conventional treatments, which have been effective include the following: wearing sunscreens, avoiding the sun, hypopigmentation agents such as hydroquinone (considered the gold standard treatment,[17] despite its toxicity), chemical *peels* and dermabrasion, and different types of laser treatments. Despite the multiplicity of all these therapies, their efficacy and safety are still controversial.[3]

Tranexamic acid (TA) is a plasmin inhibitor used to prevent fibrinolysis to reduce blood loss. Its use in melasma treatment was described for the first time by Nijor in 1979 in Japan.[2,18,19] It is a synthetic derivative of lysine and exerts its effect by reversibly blocking the lysine binding sites on the plasminogen molecule, thereby inhibiting the plasminogen activator (PA) from converting plasminogen to plasmin.[20] Studies have shown that plasminogen also exists in human epidermal basal cells and are induced by UVR, leading to melanogenesis. TA has antiplasmin activity and consequently inhibits melanin synthesis by decreasing the level of alpha-melanocyte stimulating hormone (α-MSH).[21] Consequently, it is believed that the anti-plasmin activity of TA is the main mechanism of the hypopigmentation effect of this agent. In addition, TA is similar to tyrosine in its structure, which means that it can competitively inhibit the enzymatic activity of tyrosinase.[22] A study has shown that TA can also decrease the levels of VEGF and endothelin-1, which may be responsible for increased vascularity in melasma injuries.[7] Its mechanisms of action include the following:

- Inhibiting the UV-induced plasmin activity in the keratinocytes by preventing the binding of plasminogen to the keratinocytes, decreasing the production of prostaglandins and subsequently reducing melanogenesis in the melanocytes.[21]
- Suppressing the keratinocyte-activated melanocyte pathway. The plasmin can induce the single chain urokinase PA secretion from the keratinocytes; this later protein can induce the tyrosinase activity, increased cell perimeter area, increased dendrites and keratinocyte growth, differentiation and migration. Additionally, the growth of keratinocytes surrounding melanocytes plays an important role in melanin synthesis. Tranexamic acid can be effective in the treatment of melasma by blocking these pathways.[21]
- Decreasing tyrosinase activity.[21]
- Decreasing the level of tyrosinase-related protein TRP1/2.[21]
- Reversing the melasma-related dermal changes such as vessel number.[21]

Generally, studies have shown that TA is the only treatment modality that actually prevents melanocyte activation by sunlight, hormones, and injured keratinocytes via inhibiting the PA activation system. Additionally, TA not only reduces the formation of melasma but also reduces the likelihood of recurrence after the use of other therapeutic agents.[21]

The significant adverse effects of oral TA include nausea, diarrhea, orthostatic reactions, anaphylactic shock, skin reactions, acute renal cortical necrosis, disturbances in color vision, abdominal distension, headache, tinnitus, menstrual irregularities, and, rarely, deep vein thrombosis (DVT).[10,21] Due to the serious risk of DVT, it is necessary to identify other risk factors for thrombosis before starting treatment.[7]

This study evaluated the efficacy of oral TA in the treatment of melasma in patients from Policlínica de Mogi das Cruzes/SP

2 | MATERIALS AND METHODS

This was a monocentric, randomized, double-blind clinical trial performed with patients with facial melasma selected according to the exclusion and inclusion criteria. First, the study was submitted and approved by the Research Ethics Committee.

The trial was completely randomized and was comparative, with the following two treatments: oral TA (group A) and a placebo (group B). An evaluation was performed before any treatment. The patients used the drug or the placebo, according to the randomization list. The product application followed a double-blind scheme; neither the volunteer nor the evaluator knew which treatment was used.

2.1 | Protocol

Forty-seven (47) patients from the dermatology outpatient clinic of a public service, who had facial melasma were selected for the study, agreed to participate in the study and signed the informed consent form.

The patients were evaluated for eligibility for recruitment according to a detailed list of inclusion/exclusion criteria, the results of a brief physical examination, and a review of their medical history. All patients received laboratory tests (blood count, aminotransferases, prothrombin time, and activated partial thromboplastin time). The patients were randomly divided into two groups, with both groups receiving a white coded box containing tablets for treatment. The

drug (250 mg TA) and the placebo tablets were prepared according to the international Good Manufacturing Practices.

TA was manufactured according to the Brazilian Regulatory Agency (ANVISA) procedures, number RDC 17/2010. U.SK Dermatology developed the test drug formulation (active ingredient: 250 mg TA; inactive ingredients: microcrystalline cellulose, sodium croscarmellose, calcium phosphate, povidone, silicon dioxide, talc, magnesium stearate, and purified water) and the placebo (microcrystalline cellulose, magnesium stearate, and lactose monohydrate); the analytical evaluation and stability procedures were performed according to Good Laboratory Practices. The product package was white PVDC with aluminum sealing, and the products were stored according to the instructions on the product leaflet, namely, at room temperature between 15°C and 30°C. The drug and placebo packing boxes and blisters were identified with two different codes to achieve double bind conditions, requested per and kept as confidential data by the main study investigator.

Group A received TA 250 mg orally twice daily for 12 weeks, while group B received the placebo at the same intake frequency and at the same time. In addition, patients from both groups were instructed to wear tinted sunscreen that was SPF 50 (due to the recommendation using sunscreen with an SPF greater than 30[21] and because recent studies have shown that visible light stimulates pigmentation in melanocompetent patients, potentially interfering with hyperpigmentary dermatoses such as melasma and postinflammatory hyperchromia. According to Schalka et al[23], it has been observed that only particles of large size that are therefore visible (tinted) can offer good protection against the visible light range; therefore, we opted for the use of tinted photoprotection).

The patients were evaluated after wearing the medication and were also instructed to not use any products on the treated area other than the sunscreen.

Pictures were taken. At the last follow-up visit, participants were asked to evaluate their improvement and their satisfaction with the treatment results through a satisfaction questionnaire.

2.2 | Evaluations

The evaluations were performed before and after the 12-week treatment by the following methods:

1. MASI (Melasma Area Severity Index)[24]
2. Photographic records with photographs taken in studio, blue background, Lumix Panasonic camera, with front, side, and 45° angles; these photos were analyzed by two independent evaluators, classifying the results as (Yes) for melasma improvement and (No) for lack of improvement or worsening
3. Patient evaluation with a validated questionnaire for satisfaction before and after the end of treatment (MELASQoL)[25]
4. Colorimetry was assessed with a colorimeter (Minolta Chroma Meter CR-300). This is a compact tristimulus color analyzer that measures reflective surface colors.

   The most used colorimetric method provides three variables, namely, L*, a*, b*, as the coordinates of a three-dimensional axis, where L* represents brightness ranging from 0 (black) to 100 (white), a* represents the color variation between green and red, and b* represents the color variation between blue and yellow.[24] We measured the degree of luminosity in the most prominent facial melasma lesion.

2.3 | Data analysis methodology

The results were analyzed by descriptive statistical analysis using the following methods: ANOVA, paired Student's t-test, two-proportion equality test, Kappa concordance, and p-values. The following software was used in the statistical analysis: SPSS V20, Minitab 16 and Excel Office 2010.

3 | RESULTS

Of the 47 patients selected, 37 completed the study, with 20 in group A (treatment) and 17 in group B (placebo). There was one male and 36 females. The mean age of the patients was 43.97 years old. The main reason for 10 of the previously selected patients not finishing the study was treatment discontinuation, followed by drug misuse. (Table 1).

In group A, all the patients were women, and the mean age was 45.75 years. The mean value of pre-treatment L was 54.96. All patients reported having had melasma for more than 3 years; 75% had a centrofacial pattern, and 25% had a malar pattern. In group B, 16 patients were women, and one patient was a man. The mean age was 42.88 years. The mean value of pre-treatment L was 54.55. All patients reported having had melasma for more than 3 years; 70.59% had a centrofacial pattern, and 29.41% had a malar pattern.

We compared the three scores (MELASQoL, MASI, and colorimetry) between the groups. We used paired Student's t-tests.

When we evaluated the MELASQoL, we observed a decrease in the mean prestudy value compared to the poststudy value for both groups A and B. In group A, the mean pretreatment value of 55.4 decreased to 38.2 after treatment, with a value of $P < 0.001$. (Figure 1).

With regard to the MASI score, the mean pretreatment value in group A (20.9) was also reduced when compared to the posttreatment value (10.8), with a value of $P < 0.001$. (Figure 2).

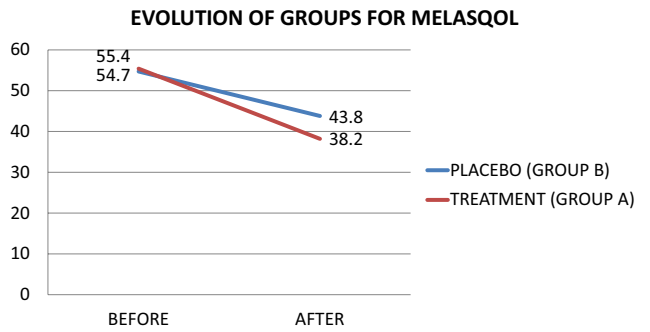
When we evaluated colorimetry, it was observed that in group A, the L value (higher values indicate lighter pigmentation) (55.0) increased after the treatment (56.1), with statistical significance ($P = 0.033$). (Figure 3).

We observed that only in group A there was a significant difference between the pre- and posttreatment values of the three scores (MASI, MELASQoL, colorimetry). In group B, significance was found only for the MELASQoL score, in which the mean fell from 54.7 to 43.8 (p-value=0.010).

When we evaluated the concordance among the evaluators for the photo analysis, we used the kappa concordance index. (Figure 4).

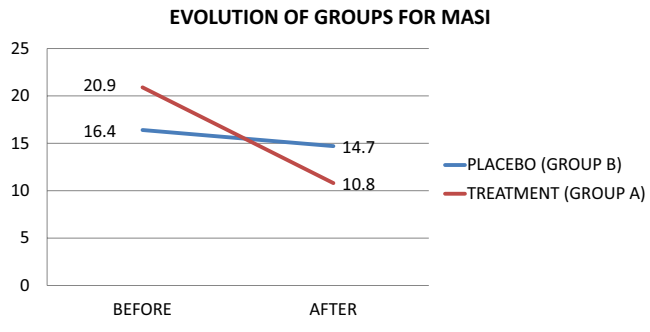
TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Men and women without comorbidities, between 20 and 60 y old	Pregnancy or intention to get pregnant during the study or <3 mo afterwards
Showing facial melasma	Breastfeeding
Absence of inflammatory dermatosis	Any chronic disease without appropriate medical control
Able and willing to fulfill all the schedule and the visit treatment and evaluation requirements	Thrombosis history
Able to understand and provide written informed consent	Smoking
	Use of oral or injectable contraceptives or hormone replacemnt therapy
	Abnormal bleeding profile
	Any medical treatment for melasma in last 30 d
	Skin resurfacing by dermabrasion, chemical peels and facial laser in the last 3 mo
	Hypersensitivity to tranexamic acid
	Unable to abstain or are unlikely to abstain from tanning during the study
	Mentally unfit, prisoner or evidence of alcohol abuse
	Participation in a drug or other device study within 3 mo prior to study or enrollment in this study
	Refusal to photographic records
	Failure to complete the whole study period
	Any condition that, in the investigator opinion, would make it unsafe for the studies or for its participants



MELASQOL	PLACEBO (GROUP B)		TREATMENT (GROUP A)	
	BEFORE	AFTER	BEFORE	AFTER
MEAN	54,7	43,8	55,4	38,2
SD	11,5	15,2	9,8	21,0
P-VALUE	0,010		< 0,001	

FIGURE 1 Comparative analysis of MELASQoL values before and after treatment in groups A and B

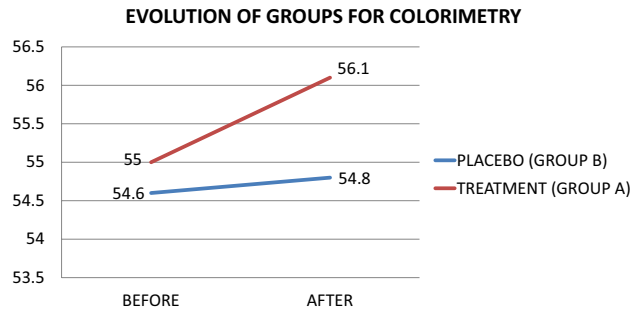


MASI	PLACEBO (GROUP B)		TREATMENT (GROUP A)	
	BEFORE	AFTER	BEFORE	AFTER
MEAN	16,4	14,7	20,9	10,8
SD	7,3	6,4	9,1	4,6
P-VALUE	0,300		< 0,001	

FIGURE 2 Comparative analysis of MASI values before and after treatment in groups A and B

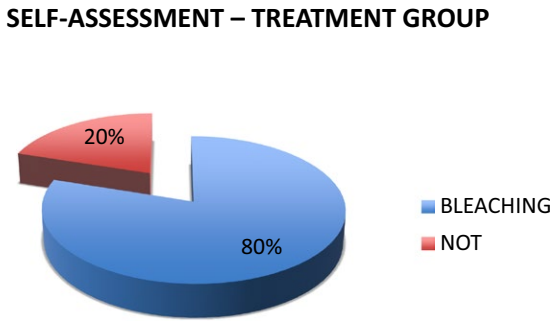
When we asked the study patients to evaluate the results, we observed that most of the patients reported melasma lightening, even patients in group B. We verified with statistical significance that 70.3% of the total patients reported lightening, whereas 29.7% denied lightening (p-value <0.001).

Among the 20 patients in group A, 16 (80%) reported melasma lightening. (Figure 5) In group B, only 58.82% reported melasma lightening.



COLORIMETRY	PLACEBO (GROUP B)		TREATMENT (GROUP A)	
	BEFORE	AFTER	BEFORE	AFTER
MEAN	54,6	54,8	55,0	56,1
SD	4,9	4,7	5,1	4,5
P-VALUE	0,810		0,033	

FIGURE 3 Comparative analysis of the values of L (luminosity) obtained with the colorimeter pre- and post-study in groups A and B



SELF-ASSESSMENT	N	%	P-VALUE
BLEACHING	16	80	< 0,001
NOT	4	20	

FIGURE 5 Self-assessment of patients in group A regarding the presence of lightening of the lesion

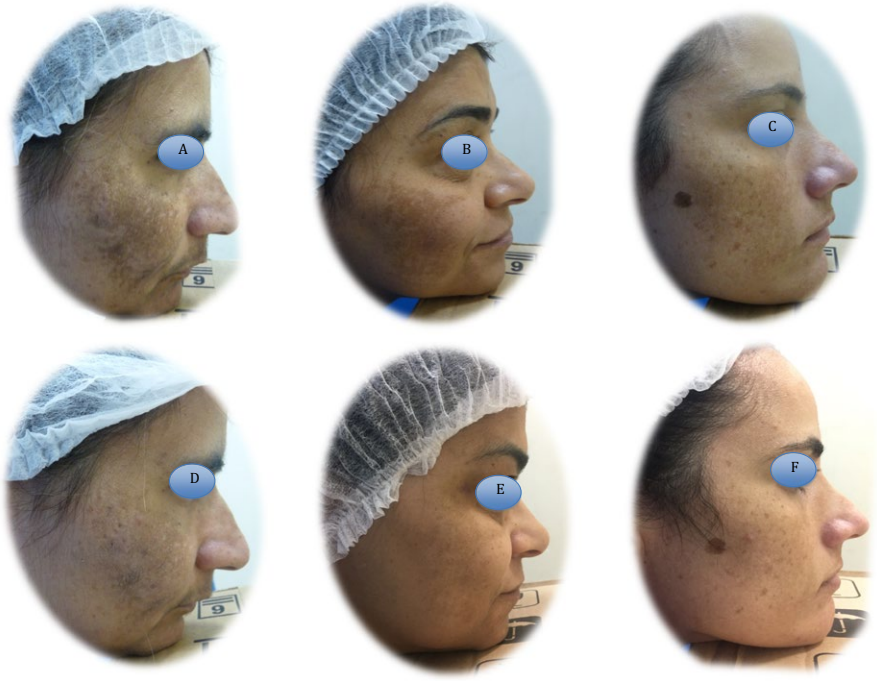


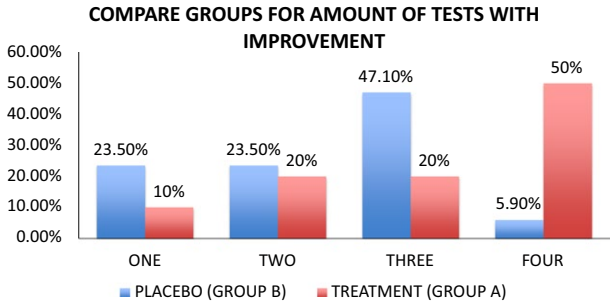
FIGURE 4 Pre- and post-study evaluation of group A. 3A, 3B and 3C: Pretreatment patients. 3D, 3E and 3F: Posttreatment patients

We compared the groups with regard to improvement/worsening distributed in each of the tests and in the tests considered together. In the situation of all tests together, if worsening was reported in at least one of the tests, it would be considered worsening in general. Thus, improvement was considered to occur only when the patient showed improvement in all four tests. We used the two-proportion equality test. Thus, in the general test evaluation, we found a 5.9% improvement in all tests in group B compared with 50.0% in group A. (Figure 6).

No patient had serious side effects during the study, and the most commonly reported side effects in group A were those related to the gastrointestinal tract (35%), such as diarrhea and nausea. The complaint of altered menstruation was also frequent (10%). (Figure 7).

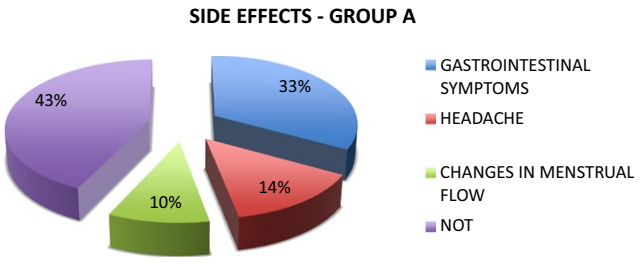
4 | DISCUSSION

Melasma is a chronic skin disease that results in facial pigmentation characterized as a brownish spot. It is more common in women than in men. It usually starts in young adults and may lead to considerable



AMOUNT IMPROVES	PLACEBO (GROUP B)		TREATMENT (GROUP A)		P-VALUE
	N	%	N	%	
ONE	4	23,50	2	10	0,266
TWO	4	23,50	4	20	0,795
THREE	8	47,10	4	20	0,080
FOUR	1	5,90	10	50	0,003

FIGURE 6 Comparative analysis of improvement in patients in both groups according to the number of tests in which they demonstrated improvement



SIDE EFFECTS – GROUP A	N	%	P-VALUE
GASTROINTESTINAL SYMPTOMS	7	33	< 0,005
HEADACHE	3	14	
CHANGES IN MENSTRUAL FLOW	2	10	
NOT	9	43	

FIGURE 7 Side effects—group A

embarrassment and distress for the patient.[22] Although several therapeutic modalities can be used, no treatment guarantees a satisfactory result. Treatment remains a challenge because the pathogenesis of melasma has not yet been fully defined, and the search for safe and effective therapies continues.[10]

The most commonly used therapy for melasma has been hydroquinone in the form of a topical cream. However, the use of hydroquinone is associated with a higher frequency of adverse effects. Compared to the use of hydroquinone in topical cream, the use of oral TA can be considered a safe and more effective therapy for melasma treatment.[2]

After searching the largest databases, such as PubMed and Cochrane, for our study topic, we confirmed that most of the studies used TA doses between 500 mg and 750 mg a day, divided into 2-3 doses, for a period ranging from 2 to 6 months. In our study, we administered a dosage of 250 mg twice a day for a period of 3 months.

Our study was one of the few to compare the use of oral TA isolated against a control group using a placebo and to evaluate the results by four different methods. We believe that this allows a more objective analysis regarding the use of oral TA in melasma with less bias than in studies that investigated other forms of treatment with fewer forms of evaluation.

The most cited evaluation tool in the studies evaluated was the MASI, usually as a single evaluation method, and only in the study by Na et al[11] was an objective evaluation method used (Mexameter® and histopathological evaluation of eight patients). Because we used four evaluation methods in our study, namely, the MELASQoL, the MASI, photographic comparison and colorimetry, with the latter being an objective evaluation method, the results of our study have greater reliability.

In our study, at the end of the 12-week treatment, we observed melasma lightening according to all evaluation scales in 50% of the patients who used oral TA, and all patients in the treatment group had improvement according to at least one evaluation scale. The study by Lee et al[10] also demonstrated improvement in melasma in 10 patients who used oral TA monotherapy. In addition, in our study, 80% of the patients treated noticed improvement in their melasma at the end of 12 weeks.

A limitation of this study was that evaluations were performed before the treatment and after 12 weeks of treatment, without intermediate evaluations. In addition, we did not evaluate the response to TA according to age, gender, chronicity, and severity of pigmentation.

The photographs were classified into only two categories, namely, yes for melasma improvement and no for the lack of improvement or worsening; this dichotomous classification may limit the accuracy of our results.

We believe that the melasma improvement seen in some patients in the placebo group was due to photoprotection and the regular use of sunscreen.

As in the study by Li et al[17], the medication was well tolerated by the patients, who presented only mild side effects such as diarrhea, nausea, and stomachache (35%), as well as changes in menstruation (10%). No patient in the study had a thromboembolic event, and all patients underwent laboratory screening prior to the introduction of the medication. We also found that of all the studies analyzed, only one had a severe event (deep vein thrombosis); later, it was verified that the patient had a familial S protein deficiency.[10] This demonstrates the safety of the medication in question when a proper pretreatment evaluation with anamnesis and laboratory tests is performed.

We conclude that TA was effective in 50% of patients according to four methods of evaluation when compared to the placebo. In addition, few and minor side effects were observed.

We also consider it important to evaluate melasma improvement using multiple methods because a greater number of evaluation tests as well as the use of objective tests allow us to draw more reliable conclusions.

We highlight the need to obtain a detailed clinical history before administering TA, in order to determine the presence

of risk factors for thromboembolic phenomena before starting treatment.

We also noticed that good medical guidance with regard to the disease and proper photoprotection is necessary for successful treatment.

Studies with a larger sample size may be needed to clearly show the results of the use of oral TA in melasma treatment.

ACKNOWLEDGMENTS

Cesário Bianchi, PhD—guidelines on article production. We appreciate the donation of tranexamic acid 250 mg treatment (Hemoblock®) and placebo provided by U.SK Dermatology/Brazil.

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How to cite this article: Colferai MMT, Miquelin GM, Steiner D. Evaluation of oral tranexamic acid in the treatment of melasma. *J Cosmet Dermatol*. 2018;00:1–7. https://doi.org/10.1111/jocd.12830