Original Article

Study evaluating the efficacy of topical and injected tranexamic acid in treatment of melasma

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ABSTRACT

Introduction: Melasma is an acquired hypermelanosis of multifactorial etiology. It is a great therapeutic chalenge. Tranexamic acid (TA) has been reported as an alternative therapy. **Objective:** To evaluate the efficacy and safety of TA in treatment of melasma, comparing the use of localized microinjection versus topical therapy. **Method:** Eighteen women with melasma were selected and divided into 2 groups. Group A: At-home topical application of TA 3% twice a day. Group B: 12 applications of intradermal injections of TA (4 mg/ml) weekly. Before and after treatment, the groups were compared according to the following parameters: photographic evolution, Melasma Area and Severity Index (MASI) evolution, self-assessment and colorimetry. **Results:** Seventeen patients completed the study. In group A, photographic evaluation showed improvement in 12,5%, worsening in 50%, and 37.5% had no change. In group B, there was improvement in 66.7% and 22.2% had no change. For the MASI, there was significant improvement ($p = 0.0026$), with no difference between treatments ($p = 0.6512$). In group A self-assessment, 37.5% of the patients rated as good and 50% as imperceptible. In group B, 66.7% rated as good and 33.3% as imperceptible. Colorimetric evaluation showed significant improvement on both treatments ($p = 0.0008$). **Conclusion:** Although the subjective clinical evaluation has demonstrated the superiority of injected treatment, in objective evaluation, both treatments were significantly effective, presenting TA as a promising new therapeutic option for melasma.

Keywords: tranexamic acid, melasma, therapy.

INTRODUCTION

Melasma is a chronic acquired hypermelanosis affecting sun-exposed skin areas, especially the frontal and malar regions.[1] It is a common condition, affecting individuals of all races and both genders, and is more observed in women of childbearing age and with higher skin phototypes (especially IV-V) who live in areas with high ultraviolet (UV) radiation.[2,3,4]

Although the etiology and pathogenesis of melasma are not completely understood, there are several factors involved. Familial occurrence in 30% of the cases suggests genetic predisposition.[1] UV radiation is an important factor, but other factors are also related, such as the use of oral contraceptives, phototoxic drugs, and thyroid dysfunction. Recently, interactions between cutaneous vasculature and melanogenesis were established.[5,6,7] However, most cases in men and one third of the cases of women present idiopathic feature.[8]

Given the high prevalence, much has been studied about the therapeutic options for melasma treatment, especially due to the possible negative psychological impact and treatment difficulty, since the condition course is refractory and recurrent. So far there is no therapy with fully satisfactory results. Steiner et al. observed in a systematic review that the use of a broad spectrum sunscreen associated with skin lightening creams, such as hydroquinone (with or without tretinoin), is the cornerstone of treatment, and new therapeutic options have emerged, requiring more studies designed to assess their efficacy.[1]

Tranexamic acid (TA), which is a plasmin-inhibitor hydrophilic drug, classically used as antifibrinolytic agent, has been studied as an alternative for treatment of melasma.[9] Recent studies have shown that its topical use prevents UV-induced pigmentation in guinea pigs[10] and that its intradermal intralesional use produces fast bleaching.[11]

TA blocks plasminogen conversion (present in epidermal basal cells) into plasmin by inhibiting plasminogen activator.[11,12] Plasmin activates the secretion of precursors of phospholipase A2, which act in the production of arachidonic acid and induce the release of basic fibroblast growth factor (bFGF). This is a potent growth factor for melanocytes.[12] Arachidonic acid is a precursor of melanogenic factors, such as prostaglandins and leukotrienes.

Plasminogen activator is generated by keratinocytes and increases the activity of melanocytes in vitro. It has increased serum levels with the use of oral contraceptives and in pregnancy. This substance blockade may be the paracrine mechanism by which TA reduces melasma hyperpigmentation.[12]

The aim of this study was to evaluate the efficacy and safety of tranexamic acid (TA) in treatment of melasma, comparing the use of localized microinjection versus topical therapy.

MATERIAL AND METHOD

This study was conducted at the Outpatient Dermatologic Clinic at University of Mogi das Cruzes and colorimetric tests were performed at a private center for clinical research.

This is an open, comparative, and randomized trial in which 18 patients were studied, aged between 23 and 52 years (mean 40.58 years, with skin phototypes II-V according to Fitzpatrick's classification and clinical diagnosis of melasma.

Exclusion criteria were clotting disorders and/or use of anticoagulant; patients with a history of intolerance to the vehicle or active substance.

All patients enrolled in the study were instructed not to apply any other product for melasma treatment besides sunscreen SPF 30 every 4 hours during the day. The patients were randomly divided into 2 groups: group A, 8 patients, at-home application of cream with tranexamic acid 3% twice/day; group B, 10 patients, application of intradermal injections with tranexamic acid 0.05 ml (4 mg / ml) in each cm² of melasma, after application of topical anesthesia with lidocaine hydrochloride 2%, once/week for 12 weeks.

Laboratory tests including complete blood count and coagulation tests were performed on all participants. Safety assessments were performed at each follow-up visit.

We evaluated the following parameters before and after 12 weeks of treatment: photographs examined by an independent investigator (classified as unchanged, presence or absence of improvement); MASI SCORE (Melasma Area and Severity Index); patient satisfaction (rating the improvement as good, imperceptible, and bad), and through an equipment colorimetry CR300 with measurements in 3 different areas (right cheek, left cheek and back of right hand as a control).

The colorimeter provides 3 variables L, a, and b, coordinate of a three-dimensional axis, where L represents brightness ranging from 0 (black) to 100 (white), a (degree of redness), and b (variation in color between blue and yellow). We also calculated the ITA (arctg [(L-50)/b)] x 180/3.1416), index that measures the skin pigmentation, where lower values indicate a darker skin and higher values a lighter skin.

Statistical Analysis

The model used for statistical analysis was linear with repeated measures, considering the measures before and after treatment in three different sites of each patient. For the model in question, we use an autoregressive correlation of 1.

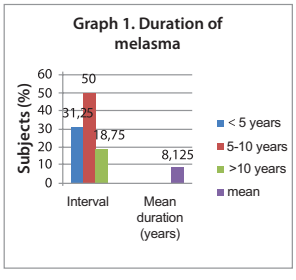
Ethical Aspects

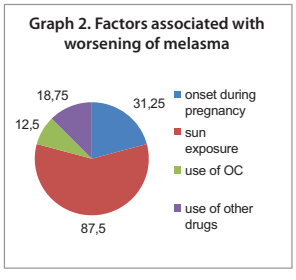
This study was conducted with the prior approval of the Research Ethics Committee and developed according to the standards of Good Clinical Practice. All patients signed an informed consent.

RESULTS

Seventeen patients completed the study, 8 in group A and 9 in group B. The average duration of melasma was 8.125 years (Graph 1), with high impact on quality of life in 50% of patients. Factors related to early pregnancy, worsening of sun exposure, and use of oral contraceptives occurred in 31.25%, 87.5%, and 12.5% of cases, respectively, (Graph 2).

Photographic evaluation showed that in group A there was improvement in 12,5%, worsening in 50%, and no change in 37.5%. In group B, 66.7% of patients showed improvement, 11.1% worsening, and 22.2% remained unchanged. Figure 1 shows examples of photographic evaluation.





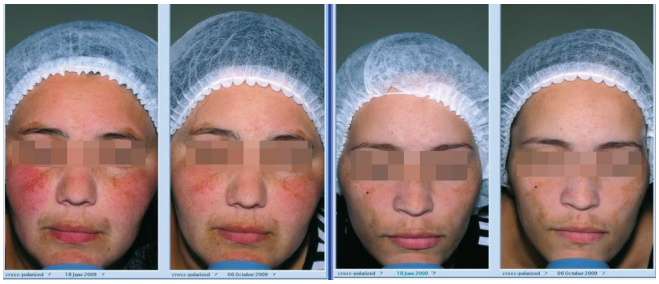


Figure 1 – Photos before and after 12 weeks of topical therapy (first two photos), and before and after 12 weeks of injection therapy (last two photos), respectively.

The MASI score had significant improvement, going on average from 12.45 to 8.84 (p = 0.0026). There was no difference between both topical and injectable treatments (p = 0.6512) (Table 1).

About the self-assessment in group A, 37.5% of patients rated melasma improvement as good, 50% as imperceptible, and 12.5% as bad. In group B, 66.7% rated melasma improvement as good and 33.3% as imperceptible.

Colorimetric evaluation showed significant improvement in both treatments, going from -6.44 to -1.56 on average (p = 0.0008). There was no difference between treatments (p = 0.8790) (Table 2).

Side effects were minimal, such as erythema, local bruising and burning, and treatment was well tolerated by patients.

DISCUSSION AND CONCLUSION

Tranexamic acid (TA) is a hydrophilic drug that inhibits the plasmin classically used as antifibrinolytic agent through oral or intravenous administration of 0.5 to 2.0 g three or four times a day. Recently, this drug has been studied as an alternative for melasma treatment by acting through its topical use as a prevention of UV-induced pigmentation in guinea pigs and producing rapid skin lightening through its intradermal intralesional use.[9,10,11]

TA blocks the conversion of plasminogen (present in the epidermal basal cells) into plasmin by inhibiting plasminogen activator.[11,12] Plasmin activates the secretion of phospholipase A2 precursors, which act in the production of arachidonic acid (a precursor of melanogenic factors, such as prostaglandins and leukotrienes) and induce the release of basic fibroblast growth factor(bFGF) – a powerful melanocyte growth factor.[12]

The plasminogen activator, which is generated by keratinocytes and has increased serum levels with oral contraceptive use and during pregnancy, increases the activity of melanocytes in vitro, and the blockage of this effect may be the paracrine mechanism by which TA decreases melasma hyperpigmentation.[12]

This study sought to address a new method of treatment using tranexamic acid in injectable solution or topical application. The mean dose of TA injected in our patients was 1.5 mg, which is lower than the usual dose used for antifibrinolytic effect, and the concentration of topical cream to 3% has minimal systemic absorption.

Both modalities were compared in several aspects, such as photographic evolution, MASI score evolution, patient's personal impression, colorimetry, tolerance to drug and vehicles.

Among the subjective assessments in group B there was a greater improvement in 66.7% of cases by photographic evaluation, compared with 12.5% of cases in group A. Difference also seen in self-assessment with 66.7% of group B patients classified as good response to treatment versus 37.5% in group A. These results are consistent with MASI results with evident improvement in the injection group. Mean MASI in group A was 12.7 to 9.9 after 12 weeks and in group B 12.2 to 7, 8, representing a percentage change of 22.04% in group A and 36.07% in group B. However, there was a statistically significant reduction in MASI after 12 weeks in both groups, with no statistically significant difference between them.

Table I - Statistical measures of MASI score for groups A and B before and after 12 weeks of treatment

		MASI				
		mean	dp	median	min	max
Treatment	**Application**					
Injection	before	12.2	5.35	10.5	5.1	19.1
	after	7.8	4.00	6.6	3.4	13.9
Topical	before	12.7	7.75	12.2	1.8	26.1
	after	9.9	7.07	8.6	2.7	25.1

Table II - Statistical measures of ITA's* index values of colorimetry in groups A and B before and after 12 weeks of treatment.
*ITA = (arctg [(L-50)/b)] x 180/3.1416

			ITA				
			mean	dp	median	min	max
Treatment	**local**	**Application**					
Injection	control	before	-12.4	13.20	-8.2	-34.2	8.2
		after	-6.6	12.69	-5.2	-24.2	12.1
	malar R	before	-3.3	18.45	-11.5	-26.4	24.3
		after	-0.5	17.95	3.6	-24.5	24.0
	malar L	before	-0.7	15.50	-0.9	-22.3	22.6
		after	1.5	20.08	-1.2	-22.9	38.0
Topical	control	before	-5.5	9.28	-6.8	-15.7	8.8
		after	-4.5	12.61	-1.6	-21.8	9.1
	malar R	before	-9.3	18.55	-10.3	-35.1	22.5
		after	-2.1	19.24	2.7	-37.8	17.2
	malar L	before	-7.4	18.87	-8.2	-32.2	21.8
		after	2.8	15.18	8.1	-20.6	19.6

*ITA = arctg[(L-50)/b)]x180/3,1416

A study by Lee *et al.* in 2006, using only subjective measures to evaluate the efficacy of tranexamic acid injection in melasma treatment, showed a decrease of 42.74% in MASI score after 12 weeks of treatment, and the patients' evaluation, 86% of them considered the results as good, and these results are similar to those found in the present study.[11]

One of the disadvantages of subjective methods of evaluation is a possible bias in clinical trials. Thus, this study has also used objective evaluation by colorimetric measure that allows quantitative analysis of pigmentation during treatment. The colorimetric evaluation showed significant improvement in both groups, ranging from -6.44 to -1.56, on average, where lower values indicate darker skin and higher values lighter skin. There was no difference between groups.

Laboratory tests of patients enrolled in the study – complete blood count and international normalized ratio (INR) – showed no changes before and after treatment. Side effects were minimal, such as erythema, bruising and local burning. Patients' tolerance to treatment showed that the treatment is safe and feasible. Although the subjective clinical evaluation has demonstrated the superiority of injection treatment, in objective evaluation both treatments were effective, with no statistical difference between groups.

In conclusion, this treatment was effective, without significant side effects. For this reason, TA is presented as a promising new therapeutic option for melasma, and can be used either as cream or injection. Further studies with a larger number of participants are needed to determine the optimal dosage, application frequency, benefits and sustained results. In addition, trials to evaluate the use of TA combined with standard treatments such as topical bleaching (hydroquinone, Kligman's formula) and chemical peelings are needed to identify any additive effects in the search for better melasma treatments.

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