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EPIDEMIOLOGICAL STUDY AND EVALUATION OF THE MELASQOL SCORE IN PATIENTS WITH MELASMA TREATED WITH ORAL TRANEXAMIC ACID OR TRIPLE FORMULA

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Abstract: Melasma is an acquired hypermelanosis, which occurs mainly on the face, affecting more women and Fitzpatrick phototypes III and IV. The pathogenesis is complex and poorly understood. Genetic background and sun exposure are classic triggers. The gold standard treatment consists of agents that interfere with the synthesis and transfer of melanin, such as the triple formula that contains 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone. Oral tranexamic acid has been studied as an alternative to treatment, as it inhibits melanogenesis and neovascularization by inhibiting plasminogen activity. This work aims to analyze the epidemiological profile and quality of life of the patients under study, with treatment with oral tranexamic acid or triple formula. We studied 24 women diagnosed with melasma, aged between 30 and 50 years, submitted to a questionnaire to assess the factors related to melasma and divided into 02 groups - group 01: oral tranexamic acid and group 02: triple formula. Photographic documentation was taken as a comparison "before and after" the intervention, and a quality of life assessment score (MELASQoL) was applied at the beginning of the study and after 60-90 days. Fourteen patients completed the 60-90 day follow-up. Ten patients dropped out of the study, nine due to absence and one due to discontinuation of treatment. Through the comparative analysis of the MELASQol of the patients in both groups at the time of inclusion and after 60-90 days of follow-up, it was possible to observe a 32.65% drop in the MELASQol of group 01 vs. 35.65% decrease in the MELASQol of group 02. Both with satisfactory results for the patients. Both oral tranexamic acid and the triple formula are drugs with a good safety profile and high effectiveness in the treatment of melasma, contributing to the improvement of the quality of life of these patients.

Keywords: Melasma. MELASQoL. Triple formula. Tranexamic acid. Therapy.

INDEX OF ABBREVIATIONS AND ACRONYMS

AT - Tranexamic acid.

RUV – Ultraviolet radiation.

VEGF - Vascular endothelial growth factor.

MELASQol - Melasma Quality of Life Scale

BIREME - Regional Library of Medicine

LILACS - Latin American and Caribbean Literature on Health Sciences

MEDLINE - Online Medical Literature Search and Analysis System

SCIELO - Scientific Electronic Library Online

SPF - Sun protection factor.

SAH – Arterial hypertension.

DM2 - Type 2 diabetes mellitus.

ACO - Combined oral contraceptive.

HRT - Hormone Replacement Therapy.

ACTH - Adrenocorticotropic hormone.

MSH - Alpha-Melanocyte Stimulating Hormone.

INTRODUCTION

Melasma is a very common diagnosis in outpatient dermatology consultations and can interfere with the patient's self-esteem and quality of life. Due to its multifactorial pathogenesis and still not fully understood, the treatment constitutes a therapeutic challenge. There is often no satisfactory response to the available therapies, even when used for long periods. Understanding the epidemiological profile of these patients allows us to indicate targeted therapeutic alternatives. Recent studies have shown promising results with oral tranexamic acid for melasma, with considerable improvement in patients' quality of life. Therefore, it is interesting to use this medication as an alternative to refractory methods, since it is a practical option and can be applied to all skin phototypes.

Melasma is an acquired hypermelanosis of the face, which mainly affects photoexposed areas. It is a very frequent entity, and is considered an important cause of emotional stress, occurring more commonly in women of childbearing age. [13] and in Fitzpatrick phototypes III and IV.[17] It is believed that extreme phototypes (I-VI) are less affected because they are stable pigmentation phenotypes.

The pathogenesis is multifactorial and poorly understood, but recent studies have shown the presence of solar elastosis, hypervascularization and an increase in mast cells and fibroblasts in melasma lesions.[12;8;21] Some of the main triggering factors for this entity include chronic ultraviolet exposure, pregnancy, female hormonal stimulation, genetic predisposition, as well as cosmetics and photosensitizing drugs.[11]

The diagnosis of melasma is fundamentally clinical. Wood's light makes it possible to distinguish between epidermal and dermal hyperpigmentation. In the case of epidermal melasma, it is possible to observe an accentuation of the color of the melasma as the light is absorbed due to excess melanin. In the case of dermal melasma, it is not possible to observe this accentuation.[5] However, recent studies have questioned this classification, since most of the time histopathological exams reveal mixed melasmas, regardless of the pattern observed in Wood's light.[1;10]

Skin pigmentation in this entity occurs by the action of melanin. This is produced by melanocytes from tyrosine, which undergoes the action of tyrosinase forming eumelanin or pheomelanin. The transfer of melanin to keratinocytes is done by the melanocyte or epidermal melanization unit.[12] Exposure to UVR promotes increased melanogenic activity, causing skin pigmentation. Infrared radiation and visible light have significantly lower melanogenic potential in normal skin. Its role in the development and maintenance of melasma is not clear, however, there have been descriptions of night workers who are exposed to the heat of ovens and professionals who are exposed to high light intensity who have great difficulty in treating melasma, referring to worsening after exposure to work.[11]

The treatment constitutes a therapeutic challenge due to its multifactorial pathology and relapsing characteristic. Current first-line treatments consist of topical depigmenting components that interfere with the process of melanogenesis and transfer of melanosomes to keratinocytes.[25] Inhibitors of tyrosinase, an enzyme that participates in the production of melanin, mainly hydroquinone, are the most used agents.[18] The triple formula, composed of hydroquinone, tretinoin and corticosteroid, is still considered the gold standard.[22] However, this chronic disease is a challenge, due to its poorly established etiopathogenesis and due to the variable effectiveness of the therapeutic options available, even the most widespread ones.[26]

Oral tranexamic acid, a synthetic derivative of lysine, used as a hemostatic agent, is an inhibitor of plasminogen activating enzyme.[19] In melasma, it acts by blocking the binding of plasminogen to keratinocytes, resulting in a decrease in tyrosinase activity.[25] It also acts by decreasing the expression of vascular endothelial growth factor (VEGF), reducing the caliber of vessels and the number of dermal vessels, also improving its vascular component.[24] Although there are studies showing improvement in melasma with topical and intralesional applications, the best results were found with oral administration of tranexamic acid, with minimal side effects, which includes virtually no thrombotic events in the populations studied.[8,21,19,4,23]Thus, it is suggested that the use of this medication does not increase the thromboembolic risk,

guaranteeing its safety profile and placing it as an adjuvant in clinical practice, with an early response and maintained in short-term follow-up.[9]

However, more studies need to be carried out in order to assess the safety profile and efficacy of this medication, which already has promising potential in the treatment of melasma, and may gain even more prominence in the near future.

OBJECTIVES

PRIMARY OBJECTIVE

To assess the level of satisfaction and improvement in quality of life, through MELASQoL, of patients with melasma after 60-90 days of starting therapy with oral tranexamic acid or triple formula.

OBJETIVOS SECUNDÁRIOS

- To analyze the epidemiological and clinical profile of patients diagnosed with melasma at the dermatology outpatient clinic of the ``Universidade Federal de Pernambuco``.
- Analyze the risk factors described in the literature for the development of melasma in each study subgroup.
- Describe the side effects presented in the studied groups.

METHODOLOGY

This is a prospective interventional monocentric study, with a quantitative and qualitative approach to the results obtained. Data collection was carried out at the Dermatology service of the Hospital das Clínicas of the ``Universidade Federal de Pernambuco``, one of the reference centers in Dermatology in the State, from June 2021 to August 2022. The study was carried out with 24 patients, of which 16 were allocated in group 01 and 08 in group 02. The patients were distributed in each group according to the indication and contraindication to the use of oral tranexamic acid.

Female patients aged 30 to 50 years, diagnosed with at least moderate melasma at the time of data collection, were included in the study. Patients who refused to participate in the study in a free and informed manner, and who did not have the time or physical and emotional conditions to provide the desired information to carry out follow-up at the institution were excluded.

DATA COLLECTION

After approval of the study by the Research Ethics Committee (CAAE:47665221.40000.8807 - Submitted on 07/20/2021) and based on the assumption that the patient signed the free and informed consent form, the patients followed at the Dermatology outpatient clinic of the Hospital das Clínicas were divided into two groups. Subsequently, data were collected through an interview (Appendix A) to assess factors related to melasma, disease duration, previous treatments, sun exposure, comorbidities, Fitzpatrick phototype, use of medication and sunscreen, among other relevant conditions.

A clinical examination and photographic documentation were also carried out in order to compare "before and after" the intervention, as well as an evaluation score - MELASQoL (appendix A) - was applied at the beginning of the study and after 60-90 days.

Inclusion criteria were female patients aged 30 to 50 years, of any Fitzpatrick phototype, diagnosed with at least moderate melasma at the time of data collection. Patients who refused to participate in the study in a free and informed manner, and who did not have the time or physical and emotional conditions to provide the desired information to carry out follow-up at the institution were excluded.

INTERVENTION PROTOCOL

Patients were allocated into two intervention groups. The first group used oral tranexamic acid at a dose of 250 mg every 12 hours for a period of 03 months. Exclusion criteria for the use of oral tranexamic acid were: female smokers, using hormonal contraceptives, with a personal or family history of thromboembolic events, or with coagulation disorders.

The second group used the triple formula, consisting of 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide at night, daily for a period of 0.05 months.

These patients were instructed to use sunscreen daily, with a Sun Protection Factor (SPF) > 50. They were instructed, first, to apply SPF without color and then with color. We also recommend reapplication of the sunscreen at 12:00 pm.

After 60-90 days of treatment, the patients were evaluated for maintenance of response, improvement or worsening, they were photographed and the same quality of life questionnaire (MELASQoL) performed at the time of inclusion in the study was applied.

STATISTICAL ANALYSIS

Data were presented using absolute frequencies and percentages for categorical variables and statistical measures: amplitude, mean, standard deviation, median and 25th and 75th percentiles for numeric variables. Initially, tests were applied to numerical variables: data normality by the Shapiro-Wilk test (in each of the groups). and equality of variances between groups by Levene's F test.

To assess the significant difference between the age groups, Fisher's exact test was used to study categorical variables and the Student test with equal variances to study numeric variables or the Mann-Whitney test.

The choice of the t-Student test with equal variances was due to the verification of the normality of the data (in each of the groups) and the equality of variances between the groups and the Mann-Whitney test in the case of sample size less than 6 cases in any of the groups. The margin of error (or the level of significance used) used in deciding the statistical tests was 5%.

The data were entered into the EXCEL spreadsheet and the program used to obtain the statistical calculations was the IMB SPSS version 25.

RESULTS

The study carried out at the Hospital das Clínicas of the ``Universidade Federal de Pernambuco`` during the period from June 2021 to August 2022 was carried out with 24 patients, of which only 14 completed the research. The 24 patients were allocated according to indication and contraindication to oral tranexamic acid. Sixteen (66.66%) patients belonged to group 01 (oral tranexamic acid) and 08 (33.33%) patients belonged to group 02 (triple formula).

All (100%) of the study patients are Brazilian and female, the mean age of patients in group 01 was 42.75 ± 4.67 years and the mean age of group 02 was 43.50 ± 4.41 years. Of the 16 participants in group 01, 03 (18.75%) had Fitzpatrick phototype II, 07 (43.75%) had phototype III, 05 (31.25%) had phototype IV and 01 (6.25%) had phototype IV. phototype V. Of the 8 participants in group 02, 03 (18.75%) had phototype II, 04 (50%) had phototype III and 01 (12.5%) had phototype V.

The prevalence of psychiatric disorders such as depression, anxiety or panic disorder among the study patients was 43.75% among participants in group 01 and 25% among participants in group 02. The data discussed above are shown in Table 01.

Table 02 describes the risk factors described in the literature associated with the development of melasma in each subgroup of

the study, according to the patients' reports. The association between the use of oral contraceptives (OC) or hormone replacement therapy (HRT) and melasma was reported by only 12.5% of patients in the oral TA group, while no patient in group 02 associated hormone use with the development from melasma. However, these findings were not statistically significant (p>0.05). Regarding pregnancy and the development of melasma, only 37.5% of group 01 and 12.5% of group 02 reported the appearance or worsening of spots during pregnancy (p> 0.05).

With regard to sunburn as a risk factor for melasma, 62.5% of patients in group 01 and 100% of patients in group 02 denied previous sunburn on the face (p=0.066). Regarding sun exposure and the appearance or worsening of melasma, 15 (93.75%) patients in group 01 and 08 (100%) patients in group 02 related sun exposure with the worsening of melasma (p=0.352). The above data are described in Table 02.

Genetic predisposition, commonly described as a risk factor for melasma, was analyzed in Table 02. In this study, 10 (62.5%) patients in group 01 reported that 1st degree relatives had melasma, 04 (25%) denied lesions similar in the family and 02 (12.5%) reported melasma in a second-degree relative. In group 02, 06 (75%) patients reported that 1st degree relatives had melasma and 02 (25%) denied similar lesions in the family.

The time of onset of melasma can be analyzed to assess the degree of response to treatment. In this research, 81.25% of patients in group 01 and 50% of patients in group 02 had melasma for more than 05 years (p>0.05). Regarding the evolution of melasma, 81.25% of patients in group 01 and 87.5% of patients in group 02 reported that the onset was gradual (p>0.05). In this research, patients were classified according to the pattern of melasma. In group 01, more than half of the patients (56.25%) had involvement > 1 region of the face, while in group 02, only (37.5%) had involvement > 1 region. However, this finding was not statistically significant (p> 0.05). These findings are described in Table 03.

During the study, 07 (43.75%) patients from group 01 left the study, 06 (85.71%) of them due to loss of follow-up and 01 (14.28%) due to treatment discontinuation. In group 02, there were 03 (37.50%) exclusions, all due to loss of follow-up.

Regarding adverse effects after inclusion in the research, in group 01, two (12.5%) patients had adverse effects, 01 (6.25%) reported headache during treatment, and 01 (6.25%) reported episodes of nausea and epigastric pain during treatment. Both reported improvement after discontinuing the medication. In group 02, all patients denied adverse effects related to treatment.

The average of the initial assessment of melasma-related quality of life (MELASQol) in group 01 was 48.22 and after 60-90 days this number dropped to 32.55. Thus, after treatment with tranexamic acid and sunscreen in patients in group 01, there was a 32.65% drop in MELASQol. Regarding group 02, whose treatment was the triple formula at night and sunscreen, the mean initial MELASQol was 46 and after 60-90 days this number dropped to 29.60, with a 35.65% reduction in MELASQol (p=0.518). The exposed data are in Table 04 and the images of the "before and after" of the treatment of both the oral TA and the triple formula are portrayed in the Figures below.

TABLES

	Tranexamic acid	Triple Formula	Value of *p*
	(n = 16)	(n = 8)	
	n (%)	n (%)	
Age			p=0,709
Range	30-50	38-49	
Average	42,72	43,50	
Fitzpatrick phototype			p=0,310
I	0	0	
II	18,75	18,75	
III	45,75	50	
IV	31,25	0	
V	6,25	12,50	
VI	0	0	
Comorbidities/psychiatric disorder			p=0,657
Anxiety, Depression or Panic Attacks	43,75	25,00	
None	56,25	75,00	

Table 01. Epidemiological data of each group analyzed in this research.

	Tranexamic acid	Triple Formula	Value of *p*
	(n = 16)	(n = 8)	
	n (%)	n (%)	
ACO/HRT association with melasma according to patient information.			p= 0,310
Yes	12,50	0	
No	56,25	87,50	
Not applicable	31,25	12,50	
Pregnancy association with melasma according to patient information.			p=0,559
Yes	37,50	12,50	
No	37,50	50,00	
Not applicable	25,00	37,5	
Previous sunburn on the face			p=0,066
Yes	37,50	0	
No	62,50	100	
Association of melasma with sun exposure according to patient information.			p=0,352
The person gets worse	93,75	100	
The person does not get worse	6,25	0	
family history			p=0,822
Nobody	25,00	25,00	
1º degree	62,50	75,00	
2º degree	12,50	0	

Table 02. Analysis of risk factors described in the literature for the development of melasma in each study subgroup.

	Tranexamic acid	Triple Formula	Value of *p*
	(n = 16)	(n = 8)	
	n (%)	n (%)	
Melasma onset time			p=0,167
< 1 years	0	0	
1-5 years	18,75	50,00	
> 5 years	81,25	50,00	
Not applicable	0	0	
melasma progression			p=1,000
Gradual	81,25	87,5	
Abrupt	18,75	12,5	
melasma pattern			p=0,616
Malar	31,25	37,50	
Centrofacial	12,50	25,00	
Jaw	0	0	
1 or > affected regions	56,25	37,50	

Table 03. Clinical characteristics of the subgroups analyzed in the research.

	Tranexamic acid	Triple Formula	Value of *p*
	(n = 9)	(n = 5)	
	n (%)	n (%)	
Adverse effects during the study			**p=0,536**
Yes	12,50	0	
No	87,50	100	

Table 04. Adverse effects of the proposed treatments for the two subgroups.

	Tranexamic acid	Triple Formula	Value of *p*
	(n = 9)	(n = 5)	
	n (%)	n (%)	
MELASQol (initial)			p=0,966
Average	48,22	46	
Range	17-66	26-57	
MELASQol after 60-90 days			p=0,732
Average	32,55	29,60	
Range	10-54	12-53	
Drop in MELASQol	32,65	35,65	p=0,518

Table 05. MELASQoL evaluation of patients with melasma treated with oral tranexamic acid or triple formula.

FIGURES

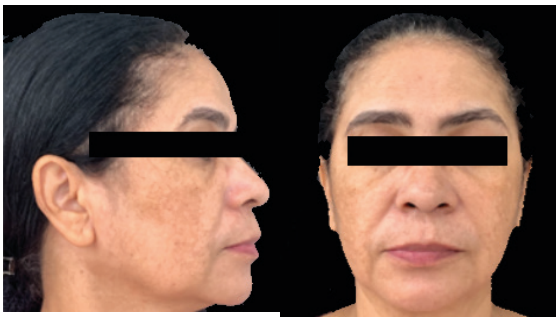

Figure 01. Melasma with frontal and malar involvement before starting treatment with tranexamic acid.

Source: the own author.

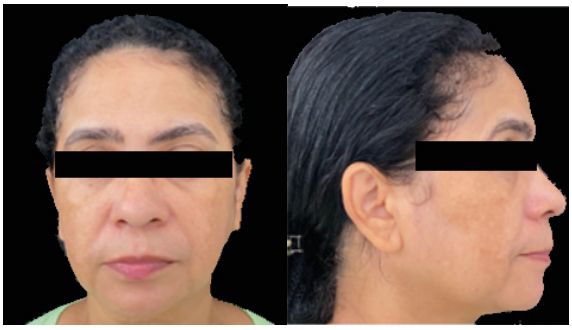

Figure 02. Reassessment after 90 days of starting treatment with TA.

Source: the own author.

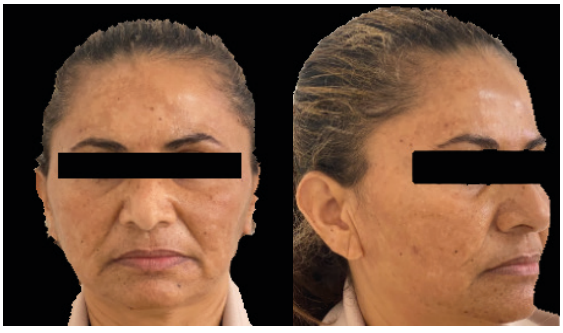

Figure 03. Melasma with frontal and malar involvement before starting treatment with tranexamic acid.

Source: the own author.

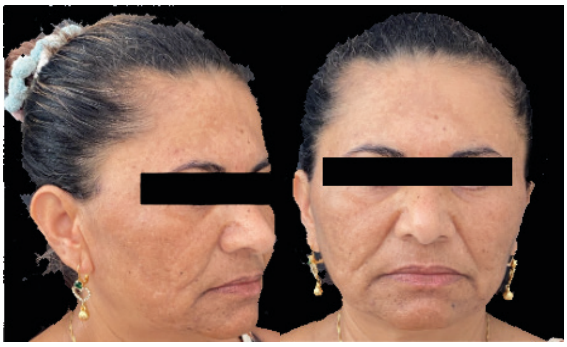

Figure 04. Reassessment after 60 days of starting treatment with TA.

Source: the own author.

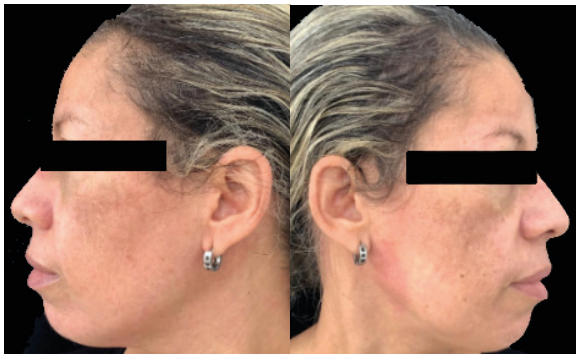

Figure 05. Melasma with frontal and malar involvement before starting treatment with tranexamic acid.

Source: the own author.

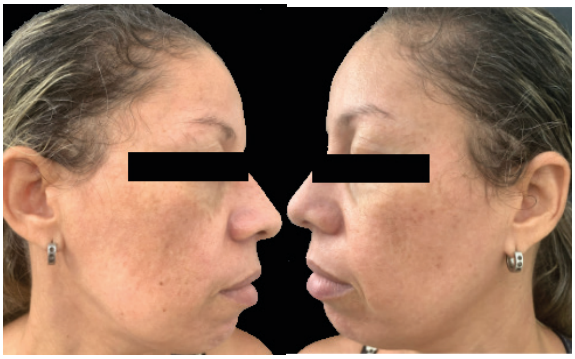

Figure 06. Reassessment 60 days after starting treatment withTA.

Source: the own author.

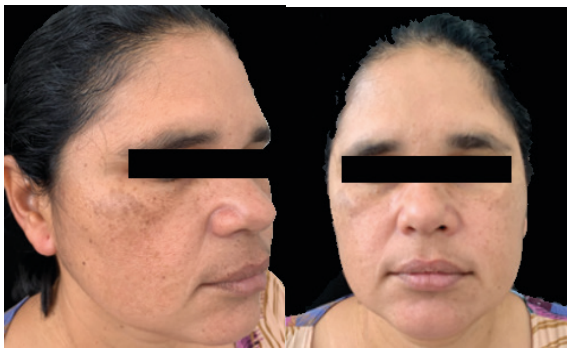

Figure 07. Melasma with frontal and malar involvement before starting treatment with the triple formula.

Source: the own author.

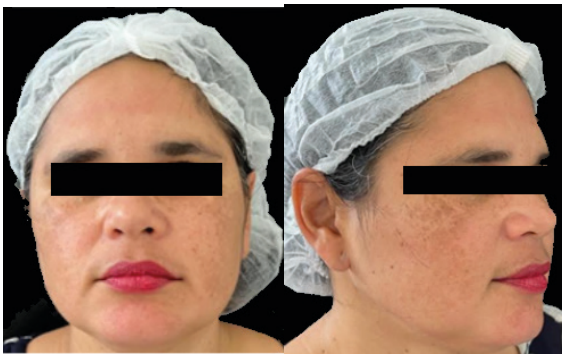

Figure 08. Reassessment 90 days after starting treatment with the triple formula.

Source: the own author.

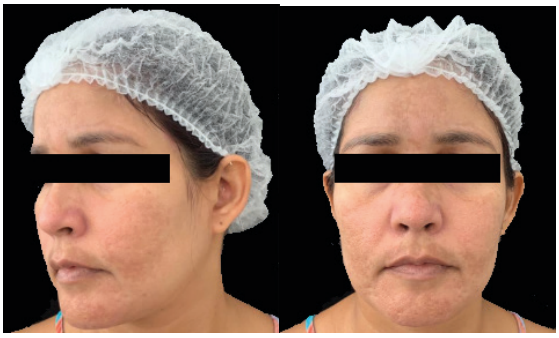

Figure 09. Melasma with frontal, malar and mandibular involvement before starting treatment with the triple formula.

Source: the own author.

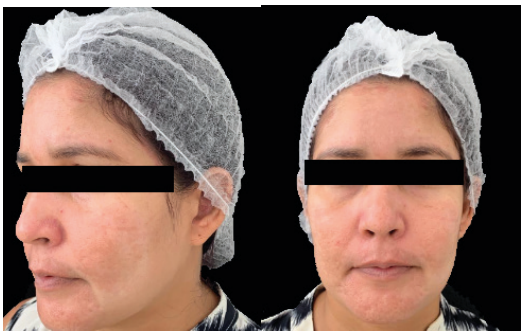

Figure 10. Reassessment 90 days after starting treatment with the triple formula.

Source: the own author.

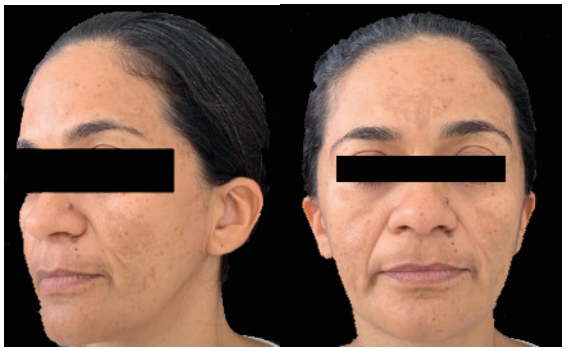

Figure 11. Melasma with frontal and malar involvement before starting treatment with the triple formula.

Source: the own author.

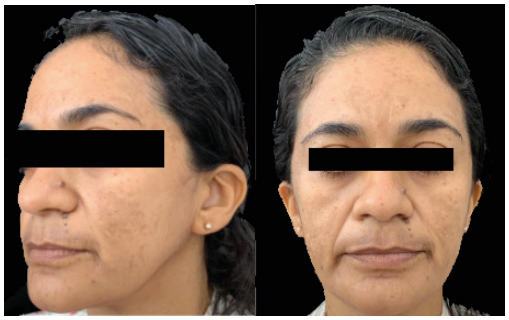

Figure 12. Reassessment 90 days after starting treatment with the triple formula.

Source: the own author.

DISCUSSION

Melasma is a common pigmentation disorder, mainly in photoexposed regions.[21] It can be classified into three distributions: malar pattern, centrofacial pattern and mandibular pattern (less frequent).[14] Similar to what most studies show, all patients in our research have melasma distribution on the face, photoexposed areas, 33.33% with malar pattern, 16.66% with center-facial pattern and 50% with involvement of more than one region, there was no patient with an exclusively mandibular pattern. The age of onset of melasma is between 30-55 years, being more common in females who represent around 90% of cases. Melasma affects individuals of all races, favoring intermediate phototypes III-V and individuals of Asian or Hispanic origin.13 The onset of the disease is earlier in light skin types, while dark skin types (V and VI) generally are associated with a late onset of melasma, and may even occur in post-menopause.[16] In this research, corroborating most of the data found in the literature, 87.5% of the patients belong to groups of intermediate phototypes III-V.

The etiopathogenesis of melasma is not fully understood. Studies demonstrate several factors that induce melanocyte activation and melanin production in melasma patients. These factors include genetic influence, sun exposure, stressful events, pregnancy, hormone replacement therapy, use of contraceptives and cosmetics.[21;11]

Genetic influence is believed to be among the main causes of melasma. This association has been suggested due to reports of familial incidence in patients with this entity.[11] Ortoone et al, in a multicenter study involving 324 patients in nine centers around the world, observed that 48% of individuals with melasma reported a family history of at least one relative with this entity and, among those with a positive history, 97% were relatives of first degree.[3] In a study carried out in Brazil with 302 patients, family history was identified in more than half of the cases (56.3%).[6] In this research, of the 24 participants, 75% of the patients reported a family history of melasma, 66.66% of which were first-degree relatives and 8.33% were second-degree relatives.

Among the triggering factors described, sun exposure is the factor most associated with the occurrence of melasma. It is believed that UVA and UVB ultraviolet radiation directly stimulates melanogenic activity, causing an increase in epidermal pigmentation, especially in the affected skin.[11;2] Sanchez et al, evaluated that most patients residing in Puerto Rico reported the onset of melasma during the summer months and worsening after sun exposure, while during the winter months, patients felt their melasma less noticeable.[14] Similar to what most studies found in the literature show, it was observed in this research that 95.83% of patients reported worsening of melasma after sun exposure.

The association of melasma with pregnancy is also described in the literature. During pregnancy, especially during the third trimester, hormones related to melanogenesis such as placental, ovarian and pituitary hormones are increased. It has even been observed that in cultured human melanocytes, estrogen induces the synthesis of melanogenic enzymes such as tyrosinase, stimulating melanogenesis.[20] Pregnancy-associated melasma tends to regress completely with adequate treatment, however around 30% may persist with some pigmentary sequelae. Including, recurrence of melasma in other pregnancies is frequent.[11] In our research, of the 18 patients who had already had at least one pregnancy, 38.88% (seven) associated melasma with pregnancy.

The use of ACO and TRH have been described in the pathophysiology of melasma with a mechanism similar to that

of pregnancy, through the stimulation of melanocytes mediated by estrogen.[15]However, there are some studies that support the use of progestogen-containing oral contraceptives, since progesterone could decrease melanocyte proliferation without significant effects on tyrosinase activity.[15] Considering the data mentioned above, in our research, only 02 (8.33%) patients related the use of hormonal medication to the development of melasma. This divergence in relation to what is presented in the literature that associates the use of these medications with the development of melasma can be explained by memory bias, since most patients were not currently using OC, or perhaps explained by the use of OC with progestogen, shown in some works as a possible protection factor.

The prevalence of psychiatric illnesses is higher in patients with a dermatological condition than in the general population. It is estimated that one third of these patients have emotional and psychological disorders such as anxiety and depression.[11,7] Stress and depression increase levels of melanogenic hormones such as cortisol, ACTH and MSH in the blood. Thus, it is evident that melasma has a cause and effect relationship with depression and stress via psychoneuroendocrine pathways. In this study, 37.5% of patients reported suffering from some type of psychiatric illness such as depression and anxiety.

The treatment constitutes a therapeutic challenge due to its multifactorial pathology, chronicity and recalcitrant characteristic. Although there are several therapeutic options such as depigmenting agents, chemical peelings and laser, many patients are refractory to these therapies, requiring more effective alternatives.[21]

Oral tranexamic acid (TA) was initially developed to be used as a hemostatic agent. However, it was observed that in Asian patients who used TA for this indication, there was an improvement in melasma.[21] AT acts by blocking the binding of plasminogen to keratinocytes, resulting in a decrease in tyrosinase activity.[25] It also acts by decreasing the expression of VEGF (vascular endothelial growth factor), reducing the caliber of vessels and the number of dermal vessels, thus improving its vascular component.[24] Although there are studies showing improvement in melasma with topical and intralesional applications, the best results were found with oral administration of tranexamic acid 0.5-2g/day, with minimal side effects, which includes practically no thrombotic events in the populations studied.[8,21,19,4,23] The most commonly cited adverse events are headache, menstrual irregularity, nausea and back pain.[21] Thus, it is suggested that the use of this medication does not increase the thromboembolic risk, guaranteeing its safety profile and placing it as an adjuvant in clinical practice, with an early response and maintained in short-term follow-up.[9]

This research sought to assess the level of satisfaction and improvement in quality of life, through the MELASQoL questionnaire, comparing the oral TA with the triple formula. With regard to MELASQol, it was possible to observe similar results in the study between the studied groups. In group 01 (oral AT), there was a 32.65% reduction after 60-90 days, compared to a 35.65% decrease in group 02 (triple formula). It must also be mentioned that oral TA was well tolerated by most patients, only two (12.5%) of the 16 participants in group 01 (oral TA) had adverse effects such as headache and nausea. There were no thromboembolic events, in agreement with the current literature. Regarding group 02, no patient had adverse effects.

The limitation of the study was due to the small number of patients, despite the fact that most scientific publications are in the range

of 10-30 patients. Probably, with a larger number of patients, it would be possible to have statistically more relevant results. As a limitation, it is also worth mentioning the socioeconomic conditions of the population in the metropolitan region of Recife, who have difficulty accessing public services and commuting. As well as the period of performance of the clinical trial, which occurred during the COVID-19 pandemic period.

Thus, as it is a study in a single center and with a limited number of patients studied, we cannot extend the conclusions of this work to the general population. Therefore, conducting new studies, preferably multicenter, with a larger number of participants and for a longer period is necessary.

CONCLUSION

In this study, there was an important improvement in the level of satisfaction and quality of life of patients, through MELASQol, in relation to both oral TA therapy and the triple formula. Corroborating data from the literature, treatment with the triple formula, which is the gold standard in melasma, showed a drop in MELASQol that was slightly greater than TA. However, this drop was not statistically significant, which reinforces that the use of oral TA in a single therapy associated with sunscreen, represents a promising potential in the treatment of this entity, including as an alternative in refractory cases. It must also be mentioned that the adverse effects associated with the 0.5-2g/day dose of TA were mild, with no occurrence of thromboembolic effects.

It is noteworthy that both oral tranexamic acid and the triple formula seem to be drugs with a good safety profile and high effectiveness in the treatment of melasma, contributing to the improvement of the quality of life of these patients.

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APPENDIX A - INITIAL FORM

HOSPITAL OF CLINICS OF ``UNIVERSIDADE FEDERAL DE PERNAMBUCO``

PROJECT MELASMA

Name:	Medical record:
Origin: Number:	Telephone:

1. How old are you (complete years)?

2. Origin:

1. ( ) rural area 2. Urban area ( )

3. Patient's Fitzpatrick phototype

1. I 2. II 3. III 4. IV 5. V 6. VI

4. What is your profession or activity?

1. Housewife 2. Student 3. Self-employed 4. Salaried 5. Retired Specify:

5. What is your schooling?

1. Non-literate 2. Incomplete elementary school 3.Complete elementary school 4.Incomplete high school 5.Complete high school 6.Incomplete higher education 7.Complete higher education 8.Postgraduate

6. Have you ever smoked a cigarette?

1. Yes, I currently smoke (__ packs/year) 2. I have smoked in the past (__ packs/year) 3.Never

7. Have you ever consumed alcohol?

1. Yes, I currently drink 2. You got drank in the past 3. Never 4.Socially

8. Have you ever had any psychiatric illness, such as depression, anxiety, panic disorder?

1. Yes 2. No - Specify:_____

9. Have you ever used systemic medications, including the pill and menopausal hormones?

1. Yes 2. No - Specify:_____

10. Are you currently on any medication, including the pill and menopausal hormone?

1. Yes 2. No - Specify:_____

11. Do you believe that any of these medications were related to the onset of melasma?

1. Yes 2. No 3. Not applicable - Specify:_____

12. How long have you been using the pill or hormone for menopause? Specify time:

1. Less than 1 year 2. from 1 to 5 years 3.more than 5 years 4. Not applicable

13. At what age did the spots appear? ( ) Specify time: _____

1. Less than 1 year 2. from 1 to 5 years 3.more than 5 years 4. Not applicable

14. Do the spots appear slowly or quickly?

1. Gradual start 2. Abrupt start

15. Are your spots getting bigger, smaller or staying the same? ( )

1. Stable 2. Increasing 3.Decreasing

16. Do you feel any kind of discomfort, with pain, itching, burning? ( )

1. Yes 2. No

17. Does anyone in your family have the same spots? ( )

1. Nobody 2. 1st degree relatives (parents, children, siblings) 3. 2nd degree relatives (grandparents, uncles, cousins)

18. Have you ever been pregnant?

1. Yes 2. No

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19. Did your spots appear or get worse during pregnancy? ( )
1. Yes 2. No 3. Not applicable
20. At what time of pregnancy did your spots appear?
1. First trimester 2. Second trimester 3. Third trimester 4. Not applicable
21. Did the spots come back with your other pregnancies?
1. Yes 2. No 3. Not applicable.
22. Have you ever consulted a doctor about spots? ( )
1. Never 2. Non-dermatologist doctor 3. Dermatologist doctor
23. What medications or procedures were indicated?
1. None 2. Retinoic Acid 3. Glycolic Acid 4. Kojic Acid 5. Hydroquinone 6. Kligman Formula 7. Azelaic Acid 8. Peel 9. Laser 10. Dermabrasion 11. Non-Kligman Formula 12. Other. 13. Not applicable 14. The person doesn't remember.
24. Was sunscreen prescribed? ( )
1. Yes 2. No 3. Not applicable
25. Did the treatment prescribed by the doctor work? ( )
1. Good 2. Average 3. Bad 4. Worse 5. Does not apply
26. Were there any complications or adverse effects from the treatment? ( )
1. No 2. Irritation 3.Burns 4.Scars 5.Stains 6. Not applicable
27. Do you sunbathe for leisure or because of work? ( )
1. Occupational 2. Leisure 3. I never sunbathe
28. Have you ever suffered sunburn on your face? ( )
1. Yes 2. No
29. Does your melasma get worse with the sun? ( )
1. Yes 2. No
30. Does your melasma get worse with stress? ( )
1. Yes 2. No
31. Melasma pattern:
1. Malar 2. Centrofacial 3. Mandibular 4. One or more regions
32. Presence of comorbidities:
1. HAS 2. DM2 3. Obesity 4. Thyroid disease. 5.Other. To specify: _____
33. Initial MelasQuol:

ANNEX A – MELASQOL QUESTIONNAIRE

		Not at all bothered	Not bothered most of the time	Not bothered sometimes	Neutral	Bothered sometimes	Bothered most of the time	Bothered all the time
1.	The appearance of your skin	1	2	3	4	5	6	7
2.	Frustration with the condition of your skin	1	2	3	4	5	6	7
3.	Embarrassment over the condition of your skin	1	2	3	4	5	6	7
4.	Depressed by the condition of your skin	1	2	3	4	5	6	7
5.	The effects of your skin condition on relationships with others (e.g. interactions with family, friends, close relationships, etc.)	1	2	3	4	5	6	7
6.	The effects of your skin condition on your desire to be with people	1	2	3	4	5	6	7
7.	Their skin condition makes it difficult to show affection.	1	2	3	4	5	6	7
8.	Skin blemishes make you feel unattractive to others.	1	2	3	4	5	6	7
9.	Skin blemishes make you feel less important or productive.	1	2	3	4	5	6	7
10.	Skin blemishes affect your sense of freedom.	1	2	3	4	5	6	7

* With the agreement of the original author -Rajesh Balkrishnan[20].