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Clinical and Dermoscopic Evaluation of the Efficacy Melasma Treatment with Oral Tranexamic Acid

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Abstract

Background: Melasma is an acquired pigmentary disorder classically manifested as hyperpigmented macules and patches distributed symmetrically on the face, neck, and rarely the upper limbs. The exact etio-pathogenesis of melasma is complex and not completely understood. Treatment of melasma includes; topical, oral, procedural or combination treatments. Tranexamic acid is a plasmin inhibitor.
Objective: To evaluate the efficacy and safety of oral tranexamic acid for treatment of melasma.
Patients and methods: The study involved 40 female patients with oral intake of tranexamic acid 250 mg, twice daily, for three months. All patients were evaluated clinically, dermoscopically and by MASI scoring before and after treatment.
Results: Results of the study revealed statistically significant improvement of melasma according to MASI score after 3 months of treatment in all patients, indicating that oral TA may be considered as a very effective treatment for melasma. As regard the response of treatment, 19 (47.5%) patients had excellent response, 12 (30%) patients had very good response, and 9
(22.5%) patients had good response. Dermoscopic features after treatment showed that, there were improvement of pigmentation and elimination of erythema as 27 patients (67.5%) showed fainting of colour and elimination of erythema, and 13 patients (32.5) patients showed light brown pigmentation and elimination of erythema.
Conclusion: Oral intake of TA is a safe and effective method for treatment of melasma, with no risk of PIH, thrombotic or bleeding tendency.
Keywords: tranexamic acid, melasma

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Introduction

Melasma is an acquired hyperpigmentation skin disorder, mostly on sun exposed areas of the face, neck and forearms. It is a frequent condition that has a considerable influence on the quality of life of affected patients [(1)].

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Females are predominantly affected, mainly during the reproductive period[2].

Based on the distribution of the facial lesions, it has been divided into: centrofacial- melasma involving the forehead, cheeks, upper lip and chin, malar- melasma Involving cheeks and nose and mandibularmelasma involving the mandibular rami [3].

The precise cause of melasma is still unknown but multiple factors have been implicated: genetic and racial influences, exposure to UV radiation, pregnancy, oral contraceptives, thyroid dysfunction, estrogen progesterone therapies, cosmetics and antiepileptic drugs [4].

Several treatment lines have been tried for melasma. Topical hydroquinone together with photoprotection, are the first-line of treatment for melasma. Chemical peels, microneedling, mesotherapy, intense pulsed light and non-ablative Q switched lasers are the most common therapeutic agents used to inhibit the production of melanin. However, the many side effects, and recurrence have limited their use [5].

The systemic use of the hormone melatonin, Glutathione; that is one of the most powerful endogenous antioxidants and tranexamic acid have been tried with variable efficacy [6].

Tranexamic acid (TA), is a synthetic derivative of lysine, that blocks the conversion of plasminogen to plasmin and thereby impedes the binding of plasminogen to keratinocytes, diminishe arachidonic acid release and decrease prostaglandin and fibroblast growth factor synthesis. Prostaglandins and fibroblast growth factor both stimulate melanin synthesis. TA also decreases mast cells activity and angiogenesis [7].

TA is currently used via a spectrum of delivery routes including topical, intradermal, through microneedling and as adjutant therapy with laser to treat melasma [8]. However, sever pain, burning, erythema, scaling, irritation, dryness and stinging are the main side effects met in these trials [9].

The efficacy of using oral TA was first described in 1979 incidentally by Nijo Sadako who noticed significant decrease of melasma severity while treating a patient for chronic urticaria by TA for 3 weeks [10].

Since then, multiple studies have searched for the efficacy of oral TA in patients with melasma [11]. The current oral dosing for melasma is, on

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average, 250 mg twice daily compared with 3900 mg daily for bleeding diatheses [8].

Dermoscopy is a useful, non-invasive diagnostic tool to examine various pigmented lesions. Melasma usually appears as diffuse reticular pigmentation in various shades of brown sparing hair follicles and sweat glands openings; called the (jelly sign). It also allows the observation of vascular component significantly in many patients [12].

Thus, it can help in differentiating melasma from other conditions with facial hyperpigmentation, differentiating epidermal from dermal melasma, especially in dark skinned individuals .It can also monitor the efficacy of any therapy used for melasma and pick up complications like atrophy, depigmentation or telangiectiasia [3].

Melasma treatment methods as hydroquinone, topical agents (azelaic acid, kojic acid, ascorbic acid and licorice extract), glycolic acid peel, low-fluence Qswitched Nd:YAG (1064 nm) laser, Intense pulsed light (IPL), and fractional resurfacing lasers. Although, all these treatments aim at reducing the formation of melanin from melanocyte (topical agents) and eliminating pre-existing melanin pigment (peeling or laser). However, they may activate melanocyte by irritation, inflammation or by injuries to keratinocyte leading to recurrence of pigmentation or postinflammatory hyperpigmentation (PIH). Tranexamic acid is nowadays the modality that can actually prevent the activation of melanocyte by sunlight, hormones, and injured keratinocyte through inhibition of the PA activation system. Also it can reduce the recurrence after other treatment modalities [13].

The aim of this study is to evaluate the efficacy and adverse effects of oral intake of tranexamic acid 500mg in 2 equal divided doses for the treatment of melasma.

Patients and methods

This study was carried out on 40 female patients with melasma, with their ages ranging from 27-50 years recruited from the Outpatient Clinic of Dermatology, Andrology and STD Department.

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Inclusion criteria:

Adolescent and adult female patients with facial melasma, Fitzpatric skin type III and IV, and any age are included in this study.

Exclusion criteria:

1- Pregnancy or lactation.
2- Females on hormonal replacement therapy or oral contraceptives.
3- Liver or renal impairment, blood disease, acute infections, coronary disease, blood coagulation problems, current treatment with blood thinning drugs, e.g., aspirin, Plavix and acquired defective color vision.
4- Patients with known drug allergy especially to the study drug.
5- Patients who received any other topical treatments for melasma in the previous month before enrollment.

Methods:

All participants were subjected to:

- Full history taking.
- Thorough general and dermatological examination; to exclude relevant systemic disorders and, to evaluate skin type, type of melasma and sites affected.
- Severity of melasma was evaluated on the basis of Melasma Area and Severity Index (MASI) score system introduced by **Karn et al.** [14].

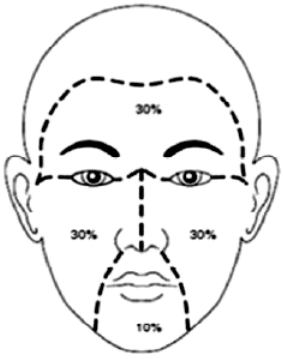

Figure (1): Melasma area and severity index

- The severity of melasma is graded according to two factors; degree of darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation.

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Darkness(D)	Homogenecity(H)
0 = Absent	**0 = Absent**
1 = slight	**1 = slight**
2 = Mild	**2 = Mild**
3= Marked 4= maximum	**3 = Marked** **4= maximum**

Figure (2): Grading of the severity of melasma

Clinical assessment:

- **Lesion distribution:** The cases were differentiated into: centrofacial, malar, and there were no cases of mandibular pattern of melasma.
- **Fitzpatrick skin phototype detection:** Depending on the Fitzpatrick scale (figure 3).

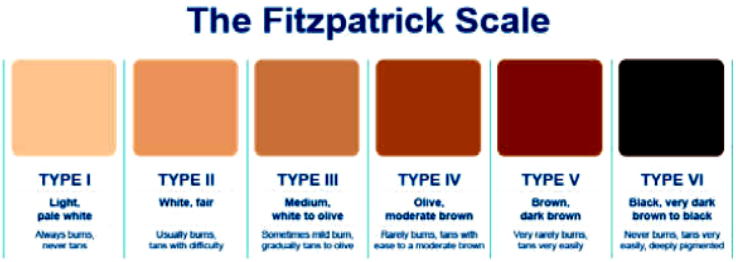

Figure (3): Fitzpatrick scale for skin phototype detection.

Wood's lamp examination: Wood's lamp examination was done for all patients to determine the type of melasma (epidermal, dermal and mixed). The used device was Waldmann DHL404 (figure 4).

Figure (4): Wood's lamp (Waldmann DHL404)

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Dermoscopic examination:

Dermoscopy was done for all patients by using Dermlite II PRO HR(3 Gen, USA) was palm sized, offered high light output, a large 25 mm 10X lens, camera adaptablility, as well as an integrated rechargeable lithium-ion battery (figure 5).

Figure (5): Dermoscope Dermlite II PRO HR3 Gen

Dermoscopic examination included:

1. Confirming our diagnosis and differentiating between melasma types.
2. Evaluating the vascular component of melasma, that was observed significantly in all patients.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test.

Significance of the obtained results was judged at the 5% level and all tests were 2 tailed.

Monte Carlo test was used for categorical variables, to compare between different groups as correction for Chi-Square when 20% of cells have count less than 5. Stewart Maxwell test was used to compare pre and post results for categorical variables.

One Way ANOVA test was used for parametric quantitative variables, to compare between more than two studied groups.

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Results

This study was carried out on 40 female patients with melasma, their ages ranged from 27 to 50 years with a mean of 36.55±6.56. The duration of melasma ranged from 1 to 5 years as 6 (15%) patients had melasma for <2 years, 22 (55%) patientshad melasma for 2-4 years, and 12 (30%) patients had melasma for >4 years. 35 (87.5%) patients were from rural areas, and 5 (12.5%) patients were from urban areas. 14 (35%) patients were worker and 26 (65%) patients were house wifes (table 1).

Table (1): Demographic characteristics of the studied cases

	n=40	%
Age/years		
Mean ± SD	36.55±6.56	
Residence		
Rural	35	87.5
Urban	–5	12.5
Occupation		
Worker	14	35.0
House wife	26	65.0
Family history		
+ve	11	27.5
-ve	29	72.5
Association with pregnancy		
+ve	23	57.5
-ve	17	42.5
Hormonal Contraceptive		
+ve	21	52.5
-ve	19	47.5
Sun exposure		
+ve	20	50.0
-ve	20	50.0
Duration/years		
<2	6	15.0
2-4	22	55.0
>4	12	30.0

Regarding the pattern of melasma, there were 25 (62.5) patients with centrofacial pattern of melasma, and 15 (37.5%) patients with malar pattern of melasma (figure 6).

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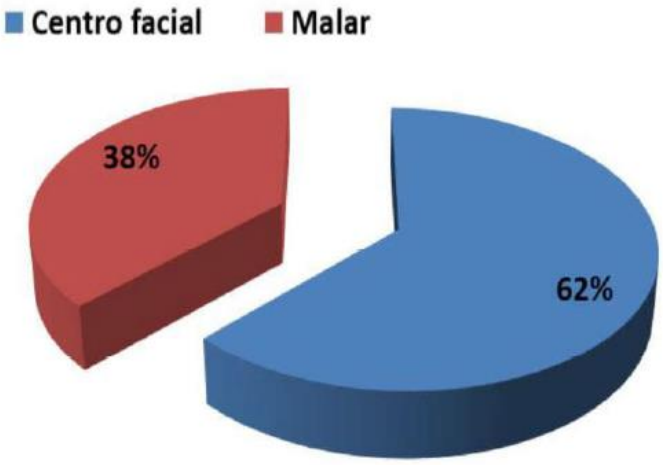

Figure (6): Pattern of melasma among studied cases

As regard the response of treatment, 19 (47.5%) patients had excellent response, 12 (30%) patients had very good response, and 9 (22.5%) patients had good response (figure 7).

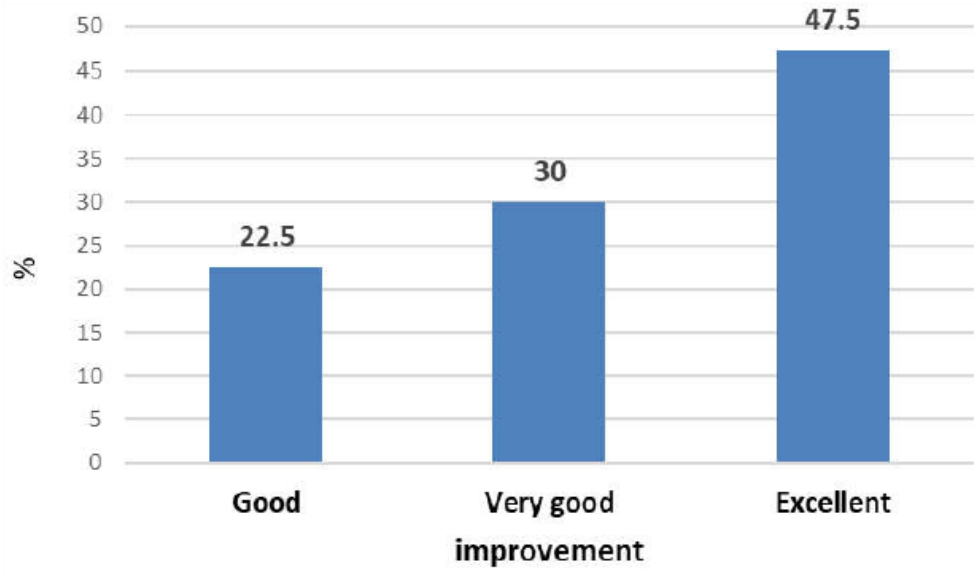

Figure (7): Improvement characteristics among studied cases

Regarding the MASI score before and after treatment with oral tranexamic acid, there was a statistically significant difference between MASI score before and after treatment (P<0.001), as shown in table (2).

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Table (2): Comparison of MASI score change between before and after treatment

MASI	Before treatment n (%)	After treatment n (%)	Stewart Maxwell test
<5	10(25.0)	40(100.0)	<0.001*
5-10	15(37.5)	0	
>10	15(37.5)	0	

*p:probability *statistically significant (p<0.05)*

Table (3) showed that there were statistically significant relations between response to treatment and hormonal contraceptives and family history. However, the relations were non-significant between response to treatment, age, residence, occupation, duration, pregnancy or sun exposure.

Table (3): Relation between improvement level and demographic characteristics of studied cases

	Improvement						Test of sig.	P Value
	Good n=9(%)		Very good n=12(%)		Excellent n=19(%)			
Age/years Mean ± SD	37.11±5.11		33.17±4.06		38.42±7.75		F=2.59	0.09
Residence								
Rural	9	100.0	10	83.3	16	84.2	MC	0.44
Urban	0	0.0	2	16.7	3	15.8		
Occupation								
Worker	5	55.6	4	33.3	5	26.3	MC	0.31
House wife	4	44.4	8	66.7	14	73.7		
Family history								
+ve	5	55.6	4	33.3	2	10.5	MC	0.03*
-ve	4	44.4	8	66.7	17	89.5		
Association with pregnancy								
+ve	4	44.4	10	83.3	9	47.4	MC	0.09
-ve	5	55.6	2	16.7	10	52.6		
Hormonal contraceptive								
+ve	7	77.8	10	83.3	4	21.1	MC	0.001*
-ve	2	22.2	2	16.7	15	78.9		
Sun exposure								
+ve	7	77.8	4	33.3	9	47.4	MC	0.13
-ve	2	22.2	8	66.7	10	52.6		
Duration/years								
<2	0	0.0	4	33.3	2	10.5	MC	0.23
2-4	6	66.7	6	50.0	10	52.6		
>4	3	33.3	2	16.7	7	36.8		

MC: Monte Carlo test *statistically significant (p<0.05)
F: One Way ANOVA test p: probability SD: Standard deviation

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Table (4) showed that there were non-significant relations between response to treatment (improvement level) and clinical characteristics of studied cases.

Table (4): Relation between improvement level and clinical characteristics of studied cases

	Improvement						Test of sig.	P Value
	Good n=9(%)		Very good n=12(%)		Excellent n=19(%)			
Type of melasma								
Dermal	2	22.2	0	0.0	2	10.5	MC	0.25
Epidermal	2	22.2	8	66.7	10	52.6		
Mixed	5	55.6	4	33.3	7	36.8		
Pattern of melasma:								
Centro facial	5	55.6	10	83.3	10	52.6	MC	0.20
Malar	4	44.4	2	16.7	9	47.4		
Flitz-skin type								
III	4	44.4	8	66.7	13	68.4	MC	0.44
IV	5	55.6	4	33.3	6	31.6		

There were statistically significant relations between response to treatment (improvement level) and dermoscopic features among studied cases (table 5).

Table (5): Relation between improvement level and dermoscopic features among studied cases

Dermoscopic features	Improvement						test of significance
	Good		Very good		Excellent		
	n=9	%	n=12	%	n=19	%	
Before treatment							
Light brown & erythema	0	0.0	4	33.3	5	26.3	MC
Dark brown & erythema	6	66.7	8	66.7	14	73.7	P=0.01*
Blue grey and erythema	3	33.3	0	0.0	0	0.0	
After treatment							
Light brown& elimination of erythema	9	100.0	4	33.3	0	0.0	MC p<0.001*
Fainting of color and elimination erythema	0	0.0	8	66.7	19	100.0	

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Regarding the dermoscopic features before treatment, there were 9 patients (22.5%) with light brown pigmentation and erythema, 28 patients (70%) with dark brown pigmentation and erythema, and 3 patients (7.5%) with blue gray pigmentation and erythema (figure 8).

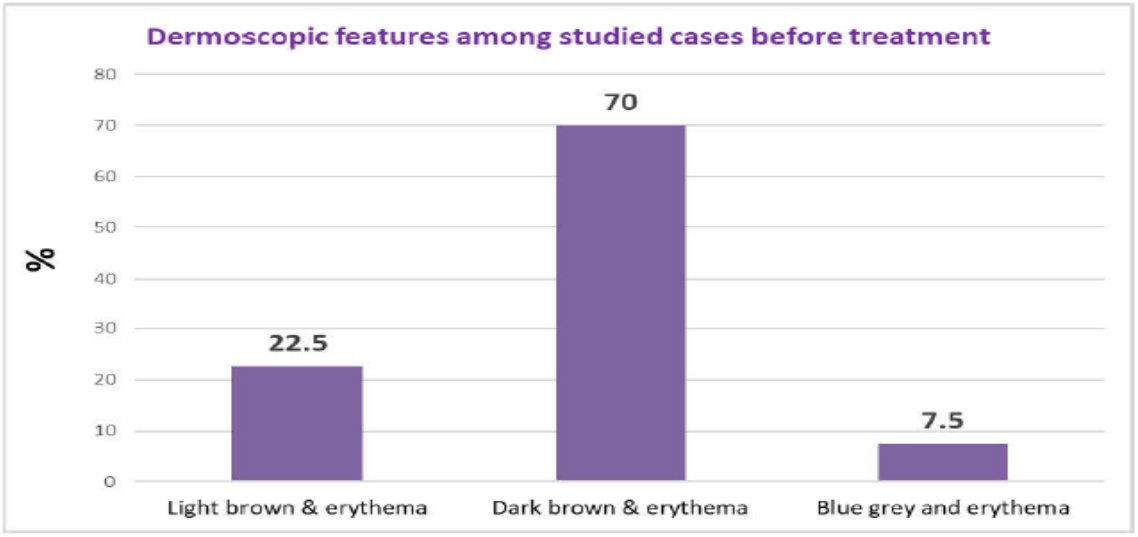

Figure (8): Dermoscopic features among studied cases before treatment

As regard dermoscopic features after treatment, there were improvement of pigmentation and elimination of erythema as 27 patients (67.5%) showed fainting of colour and elimination of erythema, and 13 patiets (32.5) patients showed light brown pigmentation and elimination of erythema (figure 9).

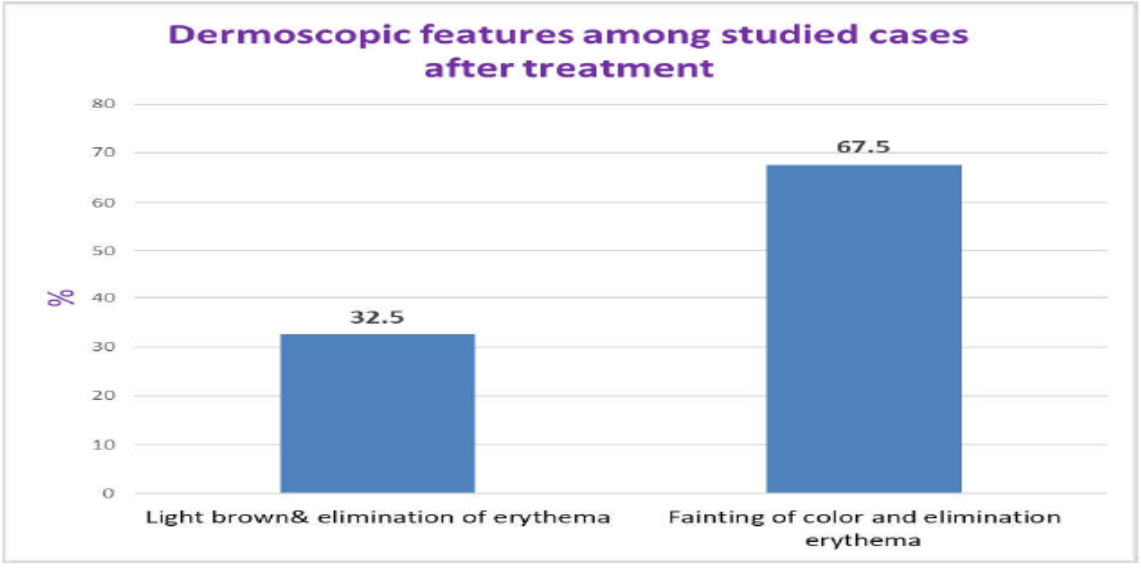

Figure (9): Dermoscopic features among studied cases after treatment

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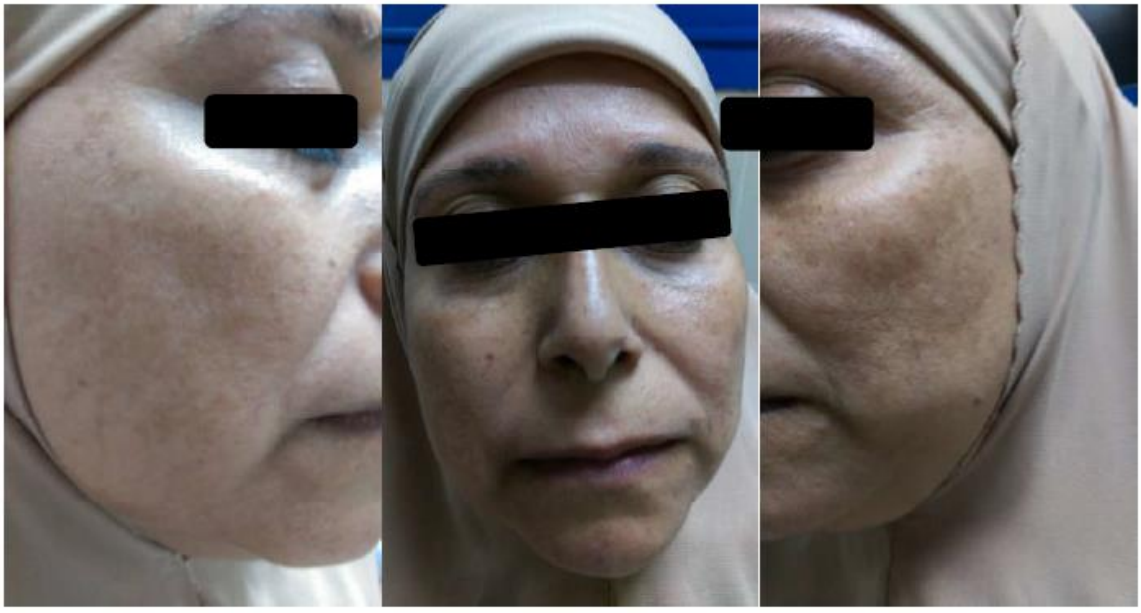
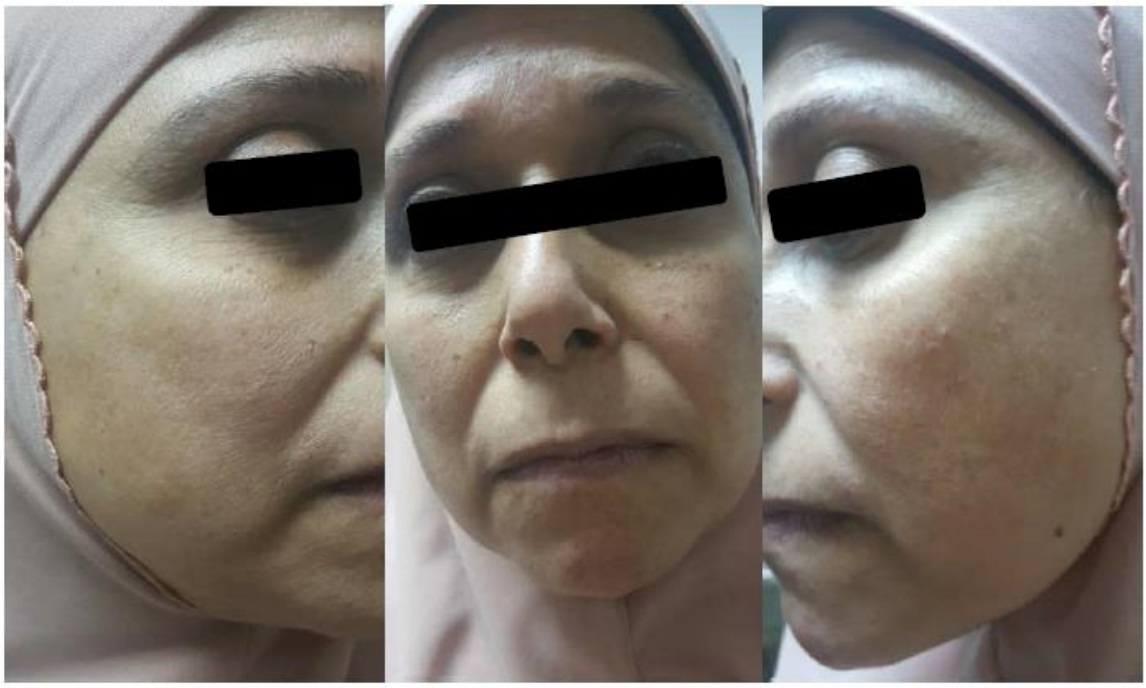
Case Number 1



48 years old female with Centrofacial melasma (MASI=10.4), before treatment



The same patients with Centrofacial melasma (MASI=0.9), after treatment with excellent response

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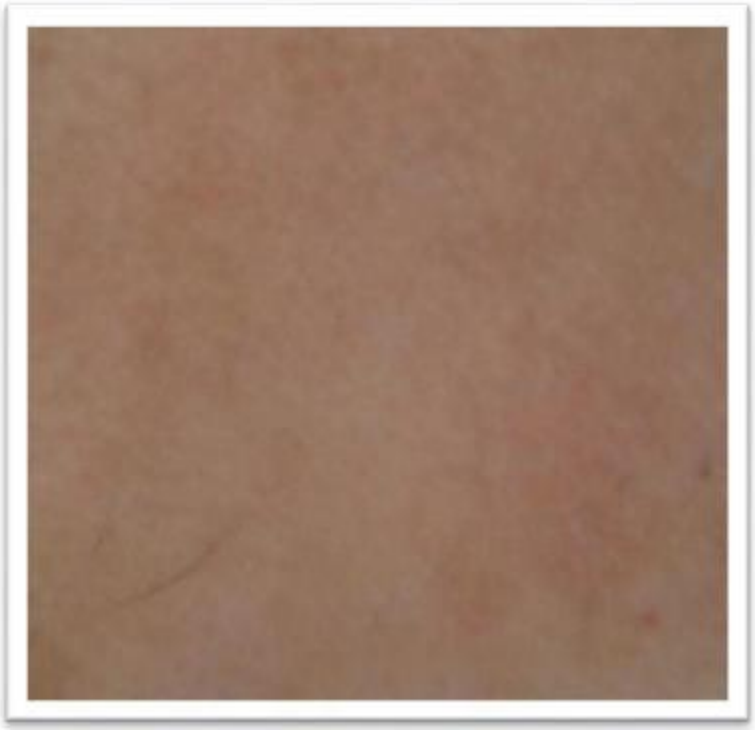
Brown regular network of pigmentation and erythema before treatment



Fainting of colour with elimination of erythema after treatment

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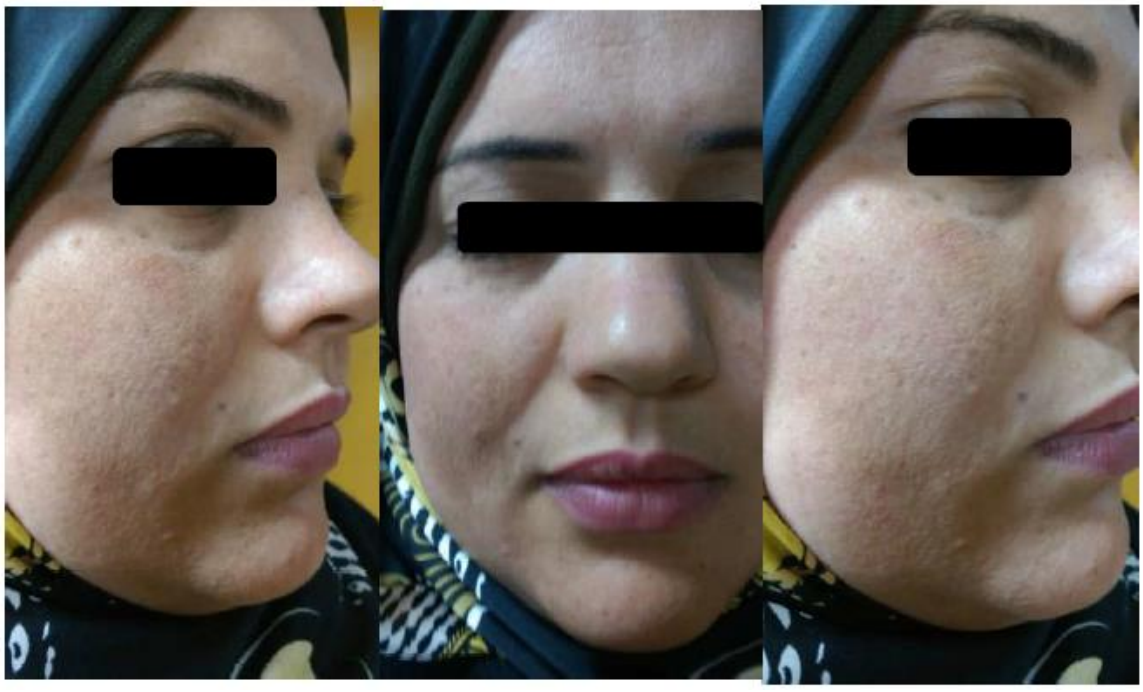
Case Number 2

39 years old female with malar melasma (MASI=7.2), before treatment



The same with malar melasma (MASI=0.6), after treatment with excellent response

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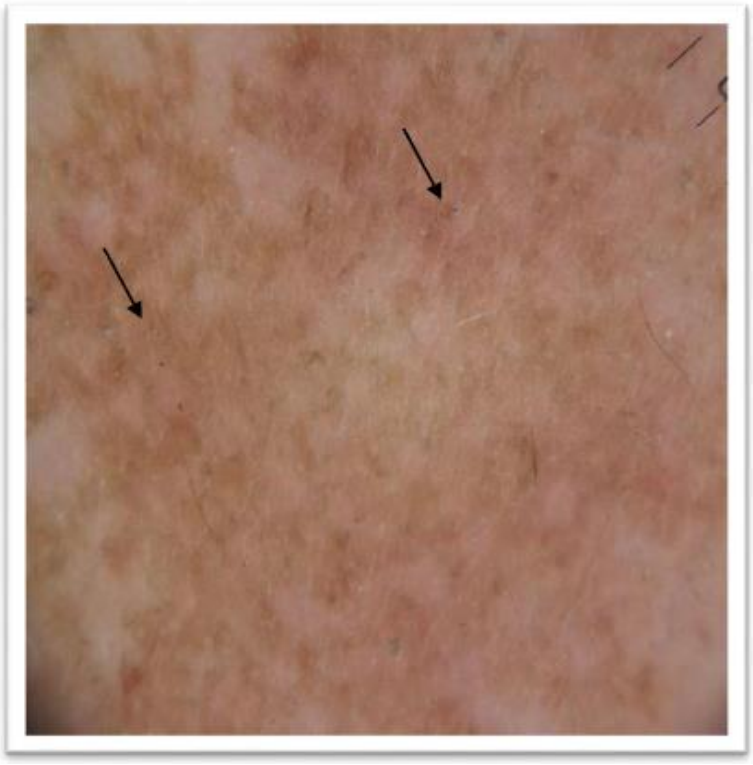
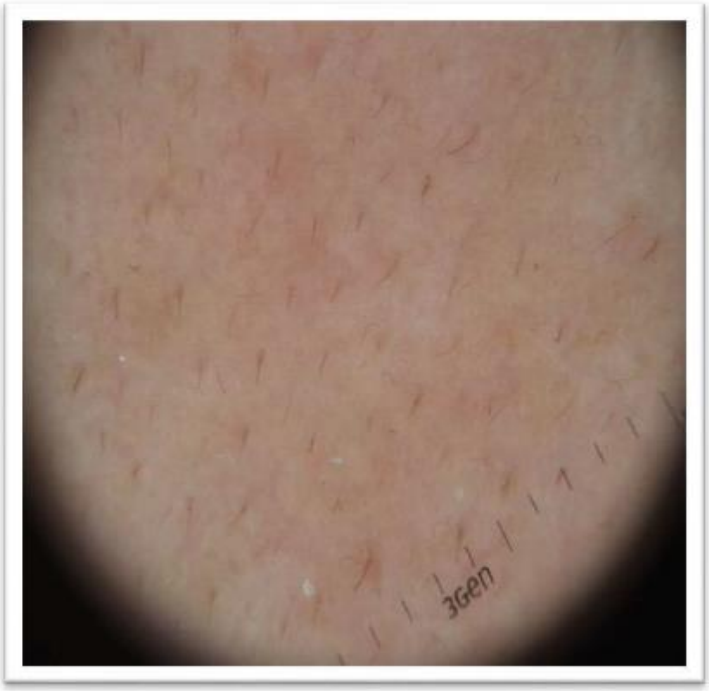


Dark brown irregular net work before treatment and erythema before treatment



Fainting of colour and elimination of erythema after tretment

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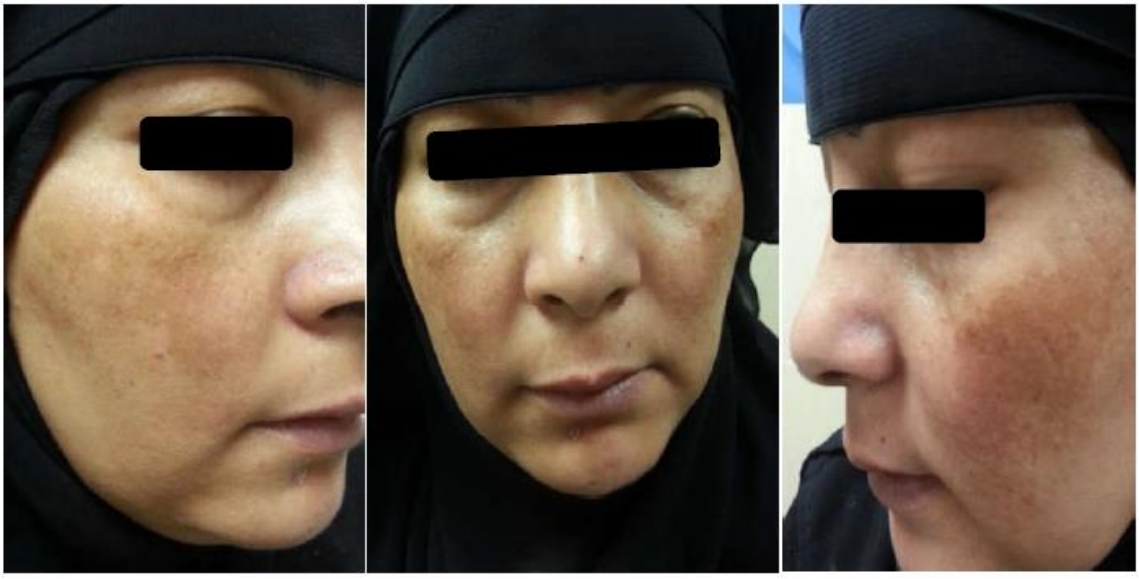
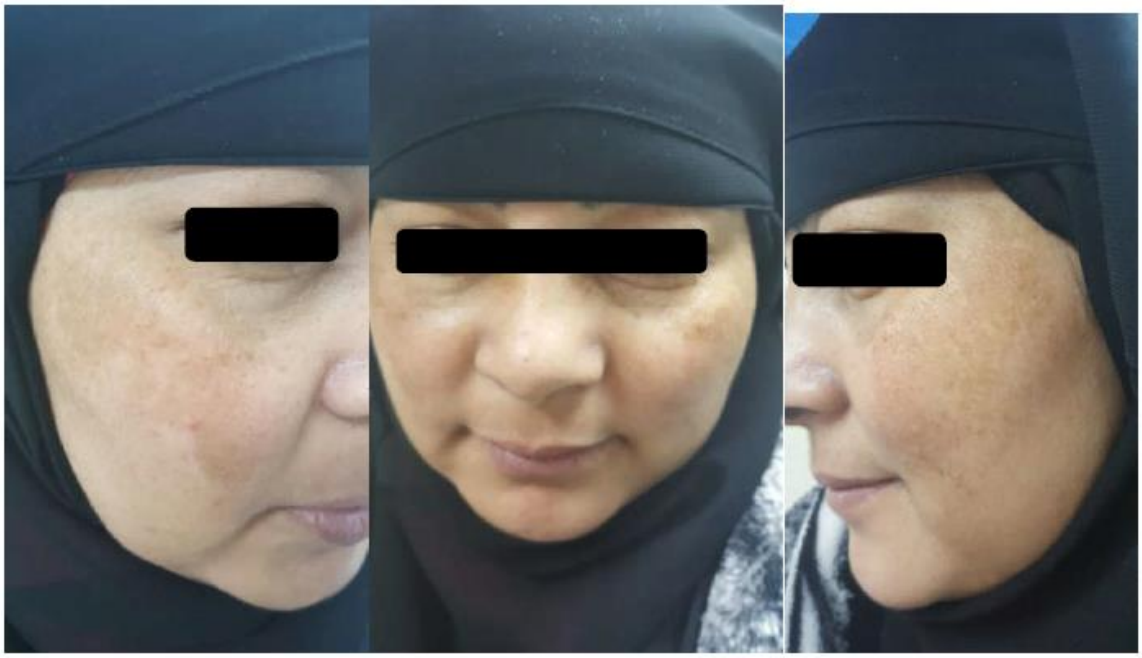
Case Number 3



40 years old female with Centrofacial melasma (MASI=8.1), before treatment



The same with Centrofacial melasma (MASI=2.4), after treatment with good response

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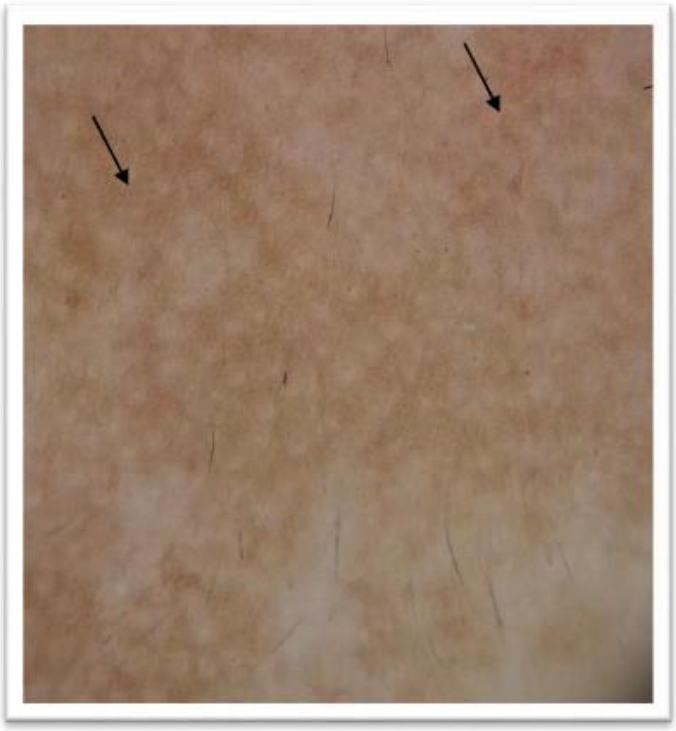
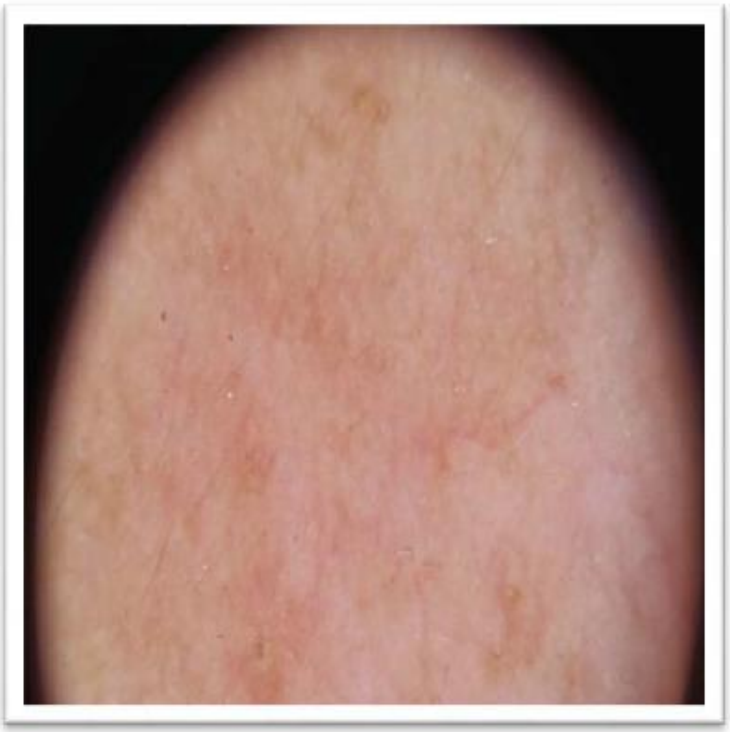


Regular dark brown network and erythema before treatment



Fainting of colour after treatment

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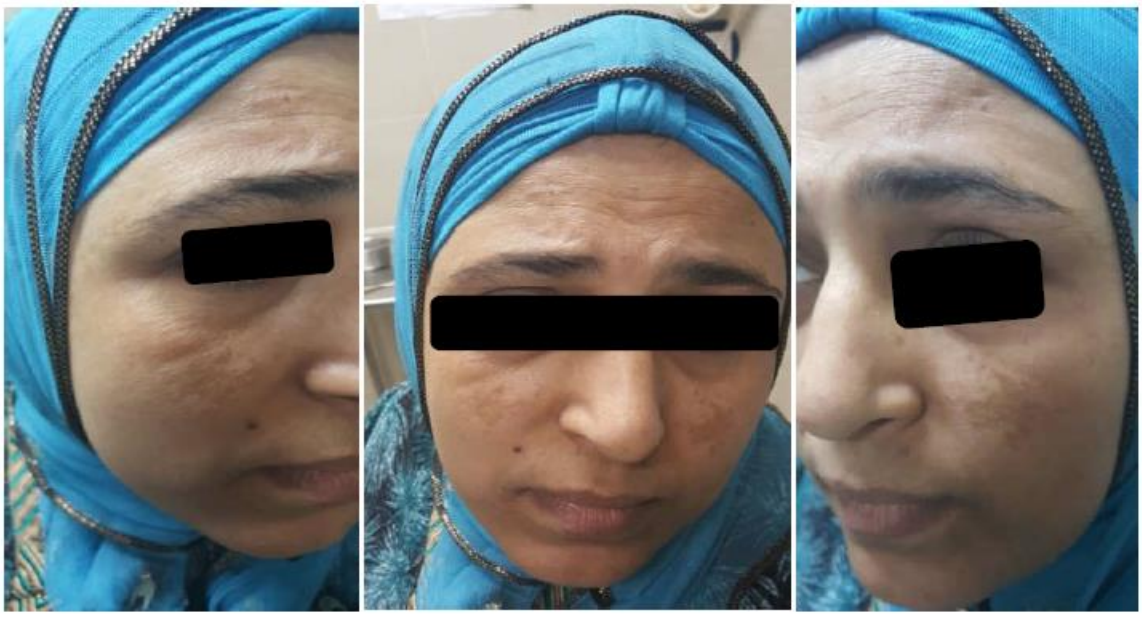
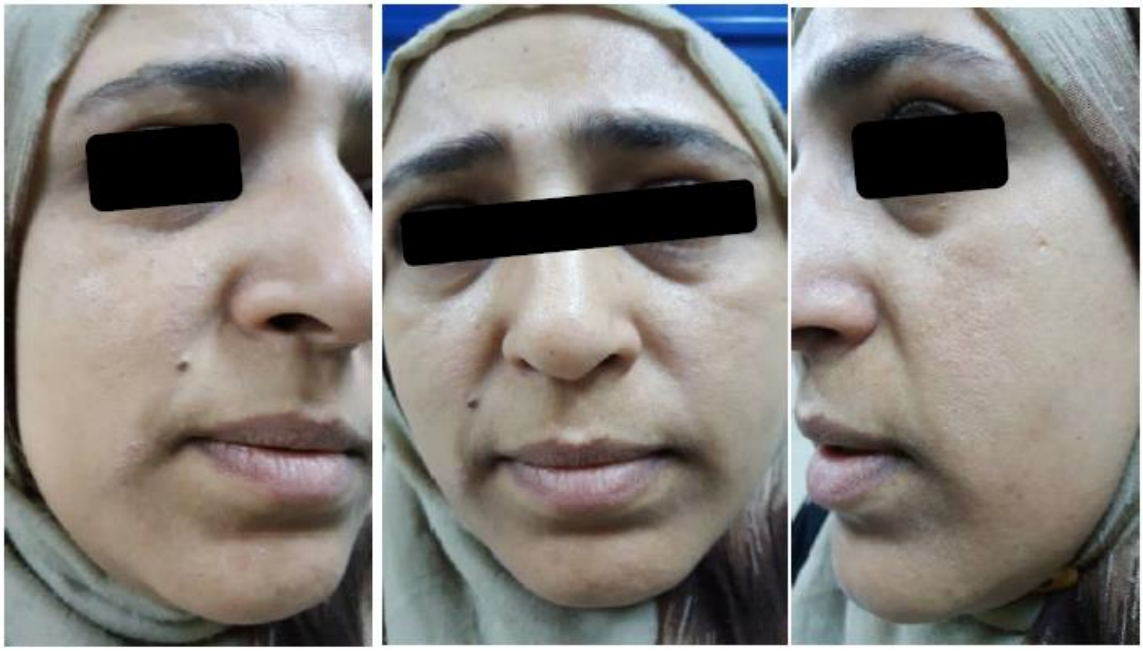
Case Number 4



39 years old female with malar melasma (MASI=3.6), before treatment



The same with Centrofacial melasma (MASI=0), after treatment with excellent response

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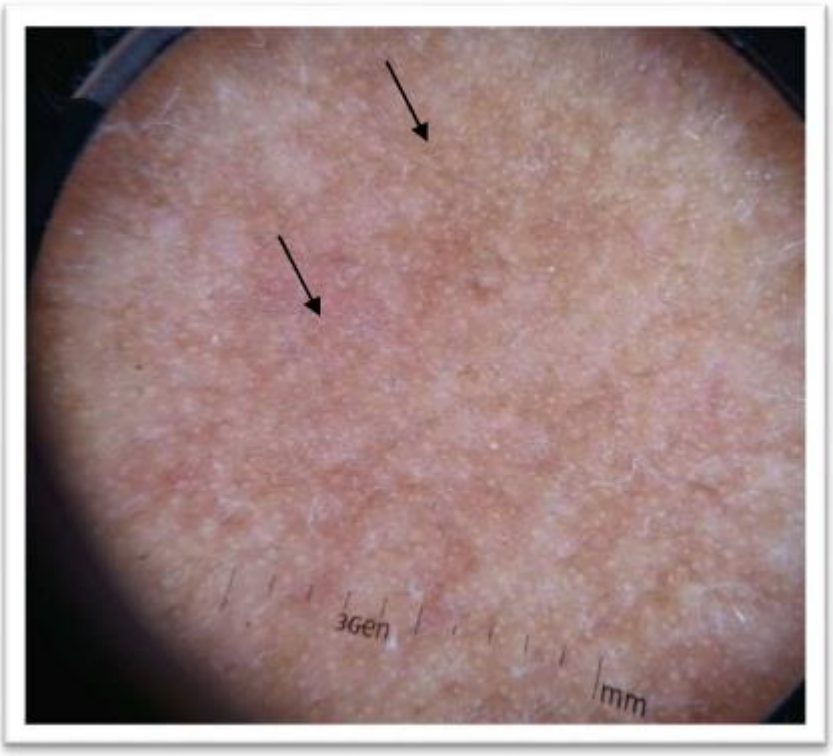
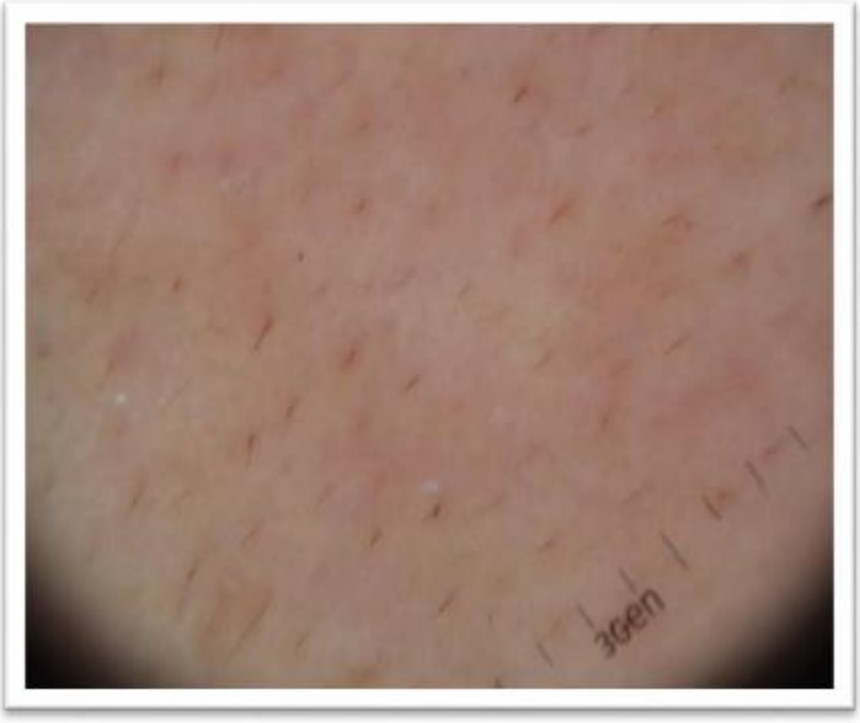


Brown network with erythema before treatment



Fainting of colour and elimination of erythema after treatment

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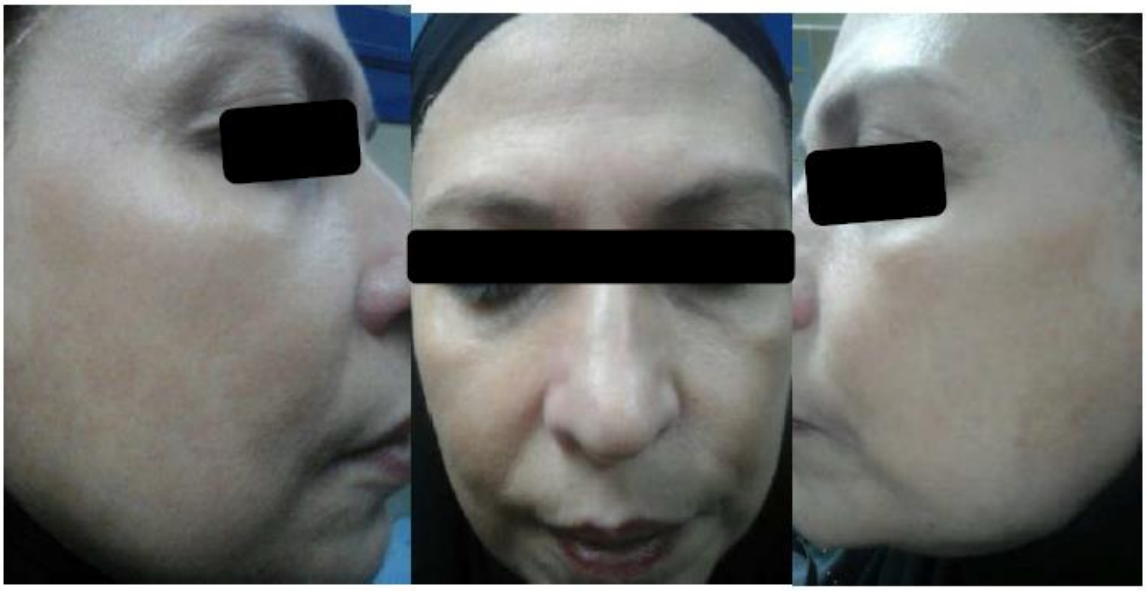
Case Number 5

50 years old female with Centrofacial melasma (MASI=13.2), before treatment



The same patient with Centrofacial melasma (MASI=2.3), after treatment with very good response

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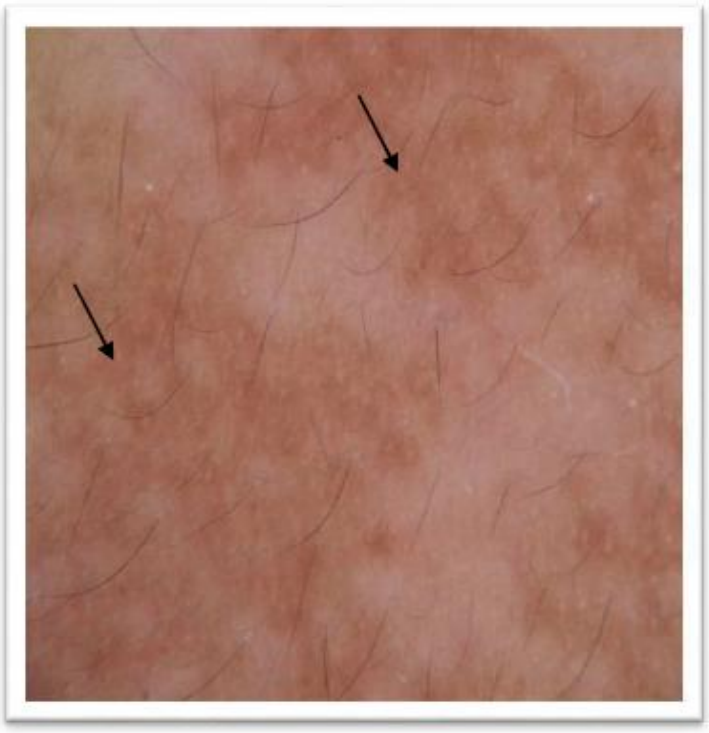
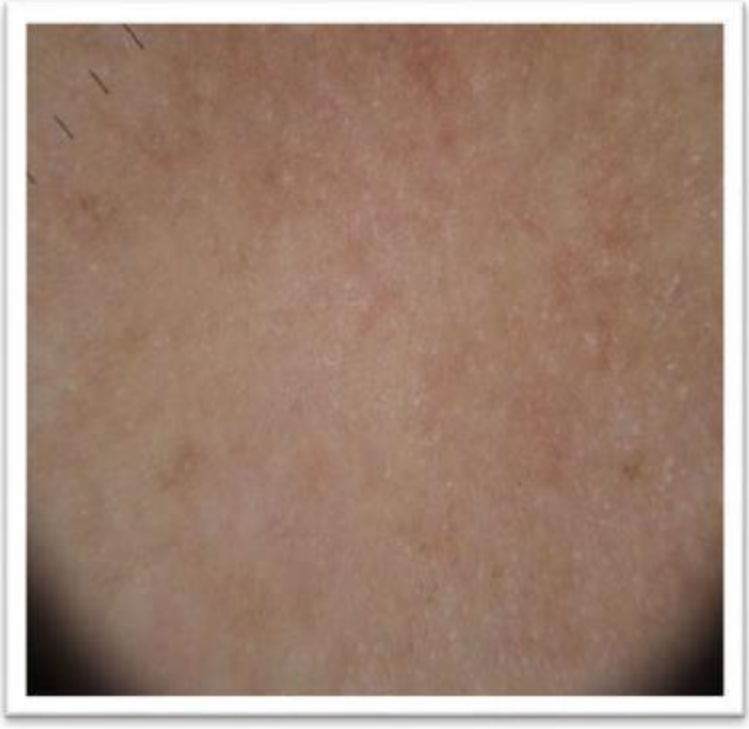


Irregular brown network and erythema before treatment



Light brown and elimination of erythema after treatment

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Discussion

Melasmais an acquired, hyperpigmentary disorder usually affecting females. It is characterized by irregular, light or dark brown macules in sun-exposed areas symmetrically involving the face, neck and less commonly, the forearms. Though the exact pathomechanism of melasma is unknown many etiological factors have been implicated in its causation and aggravation [13].

There are several therapeutic modalities used for treatment of melasma, but 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 [15].

So, our therapeutic trial was conducted to evaluate the efficacy and adverse effects of oral 500mg tranexamic acid in two equal divided doses for treatment of melasma.

Most of the previous studies used TA doses between 500 mg and 750 mg per day, divided into 2-3 doses, for a period ranging from 2 to 6 months. In the present study, patients administered TA at a dosage of 250 mg twice a day for a period of 3 months.

The duration of this study was about two years, involving 40 females. The treatment protocol included three months for treatment. Dermoscopic examination was done for whole patients before and after treatment. Digital photograghs were taken and mMASI score was done before and after treatment.

In our study, as regard the gender of the studied melasma patients, all of them were females, this was in agreement with **Jin et al.** [16]. Though it disagreed with **Sarkar et al.** [17], they interestingly found that 25.83% of Indian melasma patients were males. This was due to Indian climate and vegetables oils use after bath which may help in appearance of pigmentation in males.

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Regarding the age of the studied patients of melasma, it ranged from 27 to 50 years old with a mean of 36.55±6.56 years. Melasma predominantly appeared in females during the reproductive age. This was in agreement with **Miot et al.** [18] who stated that melasma is more common in adult women in childbearing period.

The current study showed that, history of pregnancy and hormonal contraception represented the two major predisposing factors of melasma which were found in 23 patients (57.5%) and 21 patients (52.5) respectively. History of UVR exposure was found in 20 patients (50%).

These results were in agreement with **Handel et al.** [19] as they reported history of pregnancy in (51%), followed by UVR exposure in (49%)**.** This may be explained due to hormonal involvement in the genesis of the disease, since high levels of estrogen, progesterone and melanocortin are possible triggering factors of melasma during pregnancy.

In our study, family history was found in 11 patients (27.5%), in agreement with **Nofal et al.** [20], who found positive family history in 43% of patients, therefore genetic factor could be considered as an important factor in accordance with the current results.

As regard the pattern of melasma in this study, the centrofacial pattern was the predominant pattern in 25 patients (62.5%) then the malar pattern in 15 patients (37.5%). **Grover and Reddu** [21] reported that the malar pattern was the predominant one observed in (53.3%) of cases, whereas centrofacial pattern was detected in (46.6%).

Regarding the Fitzpatrick skin phototypes, patients in the study were of darker skin types (type **III and IV**). The most common type was skin phototype III in 25 patients (62.5%) followed by skin phototype IV in 15 patients (37.5%). These results were in agreement with Soliman et al. [22] **who** reported that 60% of patients had phototype III and 40% of patients had phototype IV. It could be explained as, individuals with skin type I fail to produce additional pigmentation, and individuals with skin type VI already produce it at maximum efficiency.

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Considering the wood's light in the present study, the epidermal type was the most predominant type in 20 patients (50%) followed by the mixed type in 16 patients (40%) and dermal type in 4 patient (10%).

These results were in consistence with **Sarkar et al.** [17], who reported the predominance of the epidermal type (50%) followed by the mixed type (45%).

Increasing the vascularity is a prominent sign detected with dermoscope in almost whole patients; it is increased in longer duration of the disease and prolonged UVR exposure. **Kim et al.** [23] demonstrated that the number of vessels had a positive relationship with pigmentation in melasma lesionl skin, so it is possible to speculate that the increase in vascularity was not only an epiphenomenon of UV damage but that it may play an important role in the pathogenesis of melasma by factors released from these proliferated vessels.

Regarding the efficacy of treatment with oral tranexamic acid, there was a significant decrease in MASI score after treatment (p value<0.001). These results were in agreement with **Karn et al.** [14] who used oral TA and there was astatistically significant decrease in Melasma Assessment Sevrrity Index (p value<0.05).

Rafi et al. [24] compared the role of oral tranexamic acid 500mg/day in melasma patients with topical hydroquinone 2%, showed a significant decrease in mMASI score with systemic TA.

Malik et al. [25] Evaluated the therapeutic effects of oral TA in the treatment of melasma refractory to topical skin lightening agents in a retrospective study. The patients treated with oral TA 250 mg twice daily, in addition to pre existing combination topical therapy. Altogether 25 patients were treated with TA for a mean period of 3.7 months (range 2-8 months). The mean MASI scores after TA treatment was 69% lower than at baseline with mean onset of lightening at 1.7 months. The follow-up period was up to 6 months.

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Bagherani [26] compared the change in MASI score before and after treatment, using oral, topical and intradermally injected TA. There was high statistically significant difference after TA treatment, while there was no statistically significant difference among the three different treatment modalities of TA.

In our study, the total improvement rate was found in 100% of patient and this was in agreement with **Aamir and Naseem** [27] as the improvement rate was 98.5%. While in another study by **Lee et al.** [15], improvement rate was 89.7%.

Also, according to MASI score, 19 patients (47.5%) showed excellent response, 12 patints (30%) showed very good response, and 9 patients (22.5%) showed good response, while in a study by **Aamir and Naseem** [27]**,** the response was (23% excellent, 63% good, and 12% fair).

There were statistically significant relations between improvement and hormonal contraceptives and family history as patients without family history of melasma had better response rates than those with family history and this was in agreement with Lee et al. (2016)**.** But, there were no relation between improvement and age, occupation, pregnancy, sun exposure, type of melasma, lesion distribution or duration.

Concerning the side effecs in the present study, there were no adverse effects observed in the patients. In accordance with our results was those of the study by **Lee et al.** [15] in which side effects were reported in (7.1%), and most side effects were mild. In another study by **Li et al.** [28]**,** the medication was well tolerated by the patients, except for mild side effects such as diarrhea, nausea, and stomachache (35%), as well as changes in menstruation (10%).

Regarding the dermoscopic features before treatment there were 9 patients (22.5%) with light brown pigmentation and erythema, 28 patients (70%) with dark brown pigmentation and erythema, and 3 patients (7.5%)

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with blue gray pigmentation and erythema so the dermoscopy is considered agood classification method for melasma ad it also, allows the observation of an important vascular component. These results agreed with **Tamler et al.** [29] as it was clearly possible to observe the pigment components, as well as their position on the skin layers so dermoscopy allowed an objective classification of melasma. These results disagreed with **Hammerschmidt et al.** [30] who considered dermoscopy was not agood classification method.

As regard dermoscopic features after treatment there were improvement of pigmentation and elimination of erythema as 27 patients (67.5%) showed fainting of colour and elimination of erythema, and 13 patiets (32.5) patients showed light brown pigmentation and elimination of erythema.

There was a significant relation between improvement level and dermoscopic features among studied cases $P < 0.001$. Therefore, dermoscopy is an applicable and an appropriate method for routine diagnosis, assessment and monitoring of patients on treatment.

Dermoscopy also allows the observation of significant vascular component in many patients, which may be relevant in terms of future prospects for pathogenesis and therapeutic considerations.

The course duration was 3 months to avoid patient loss of compliance. Therefore, it may be concluded that, oral TA is safe and effective treatment of melasma. However, further studies with more prolonged duration are recommended for better evaluation.

Conclusion

Oral intake of TA is a safe and effective method for treatment of melasma, with no risk of PIH, thrombotic or bleeding tendency. In addition, this method is non-invasive and non expensive.

Dermoscopy is an applicable and an appropriate method for routine diagnosis, assessment and monitoring of patients with melisma on treatment.

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