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ORIGINAL ARTICLE

Comparison Between Intralesional Triamcinolone and Kligman's Formula in Treatment of Melasma

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ABSTRACT

Background: Melasma, a commonly acquired hypermelanosis, characterized by irregular brownish macules distributed symmetrically on areas exposed to the sun such as the face, particularly over the forehead and malar areas, and extra facial sites such as the neck and forearms. Certain inflammatory cytokines like IL6, IL1a, IL 1b, PGD2, PGE2, and PGF2 are involved in melasma pathogenesis. Corticosteroid suppressive effect on these cytokines may explain its therapeutic effect in melasma treatment. The of the study is to assess the efficacy and safety of Intralesional Triamcinolone versus Kligman's Formula in Treatment of Melasma.

Methods: This study was conducted on 44 female patients at outpatient clinic of Dermatology, Venereology and Andrology Department at Zagazig University during the period from December 2017 till November 2018. Forty-four female patients with melasma were divided in to two groups; group1 (treatment group) included 22 patients who were treated by intralesional injection of triamcinolone acetonide at a concentration of 4 mg/ml once monthly for four sessions as a maximum and group 2(control group), included 22 patients who were treated by Kligman's formula once daily for 3 months. All patients were evaluated by dermoscope before treatment and at each follow up visit to record any adverse effects of treatment. A written informed consent was taken from each subject after explaining to them the details about the nature of study and after obtaining approval from Institutional Review Board (IRB). IRB approval number is (4452).

Results: the severity of melasma, assessed by MASI score, significantly decreased in both groups at the end of third month. There was no statistically significant difference in the therapeutic response between both groups. No side effects were reported with triamcinolone injection except for mild pain during injection, while Kligman's formula was associated with dermatitis, irritation and burning sensation.

Conclusions: Intralesional triamcinolone microinjection could be a novel, preferable and harmless treatment method for melasma.

Keywords: Melasma; Melanin; Cytokines.

INTRODUCTION

Melasma is a condition of hyperpigmentation and demonstrated by more or less symmetrically distributed brownish to greyish macules and patches with edges arranged irregularly. Areas which are exposed to the sun are more prone to get melasma and usually occur in women who are young and middle-aged. The most common site where melasma occurs is the face and, less frequently, on extra facial sites for example the neck, arms, and chest [1]**.** It is usually associated with a bad effect on patient's psychological state and their quality of life [3]**.**The etiopathogenesis of melasma is not completely known. The most common factors include genetic predisposition, pregnancy, oral contraceptives, endocrine dysfunction, hormonal therapy, drugs that contain phototoxic agents, and anxiety. The major triggering or irritating factor for melasma is exposure to ultraviolet light [2].

Melasma is mainly due to excess production of melanin or an increase in the activity of melanocytes in the skin [3].

Treatment of melasma is still a challenge in spite of presence of different treatment modalities. The main targets in the treatment of melasma are

suppression of the activity of melanocytes, decrease the formation of melanosomes and accelerate their degradation [4].

Topical lightening agents are considered as the gold standard treatment for melasma. The Kligman formula (hydroquinone5%, tretinoin 0.1%, and dexamethasone 0.1%) is the most effective treatment, especially in its stabilized form. The triple combination can interfere with tyrosinase activity through hydroquinone, whereas retinoic acid and the corticosteroid can respectively exert an "anti-aging" effect and action against the mild inflammation of photo damage [5].

Certain inflammatory cytokines, for example interleukin (IL)1a, IL 1b,IL6, vascular endothelial growth factor (VEGF), prostaglandin (PG)D2,PGE2, and PGF2 are involved in the pathological process of melasma and could affect the behavior of melanocytes in the lesional area, hence suppression of these cytokines by the effect of corticosteroids has been suggested to explain the therapeutic effect of triamcinolone (Egyptian International Pharmaceutical Industries Company) in melasma treatment [6].

This study was conducted to evaluate the efficacy and safety of intralesional triamcionolne versus Kligman formula in the treatment of melasma.

METHODS

This study was a clinical trial conducted on 44-woman patients at outpatient clinic of Dermatology, Venereology and Andrology Department at Zagazig University during the period from December 2017 till November 2018. Each subject wrote informed consent after explaining to them the details about the nature of study and after obtaining approval from Institutional Review Board (IRB).IRB approval number is (4452).This study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.In this study 44 adult female patients with different types of melasma were included. Inclusion criteria are young women with mild, moderate or severe melasma and

patients with all melasma types will be included in the study. Exclusion criteria are pregnancy, autoimmune disease, women taking hormonal treatment such as oral contraceptive pills, the presence of atrophy or telangiectasia of the skin at melasma site, presence of hypersensitivity to some of the components of the formulas of the study, diabetic patient**,** coexistence of associate diseases and other pigmentation diseases and concomitant use of systemic treatments.

Forty-four female patients were divided in to 2 equal groups:

Group 1(Treatment group) included 22 patients who were treated by intralesional triamcinolone dermal injection at a concentration of 4 mg/ml by an insulin syringe, 1 cm apart between injected points with a maximum dose of 20 mg per session. The treatment was repeated monthly until complete clearance of melasma or for a maximum of four sessions.

Group 2 (Control group) included 22 patients who were treated by Kligman's formula, (hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%), at night daily for 3 months as a maximum.

Complete history was taken from all patients containing personal history (name, age, occupation and marital status), beginning of melasma, duration, family history of melasma, effect of pregnancy or sun exposure, previous treatments (e.g. chemical peelings, whitening creams or laser) and history of systemic diseases e.g. thyroid diseases.

Complete clinical examination including: General examinations to detect any other affected sites, dermatological examinations to asses type of the skin, melasma pattern (Centro-facial, malar or mandibular), the type of melasma (epidermal, dermal or mixed) by using wood's light, Dermoscopic examination(DL3 dermlite dermatoscope) of all cases was done before start of treatment and at each follow up visit.

Patients received intradermal triamcinolone injection with concentration of 4mg/ml by an insulin syringe, and 1cm apart between injected points with a maximum dose of 20 mg per session. The treatment was repeated monthly until complete clearance of melasma or for a maximum of four sessions. We used very low concentration of triamcinolone (4mg per cc) to decrease side effect of it. The severity of disease was assessed by melasma area and severity index score (MASI Score) [10].

The first scoring system to try to objectively score and measure the response of melasma treatment in a clinical trial by taking into account both the area involved, as well as the darkness of the melasma was probably the MASI score.

The therapeutic response to both treatment modalities was assessed according to the percentage of decrease of MASI scores at the end of treatment and according to the grade of patient satisfaction. The therapeutic response was scored into:

No response: (no decrease in MASI). Poor: MASI decreased by 25% or less.

Moderate: MASI decreased from 25 to 50%. Good: MASI decreased from 50 to 75%.

Excellent: MASI decreased by more than 75%. Adverse effects to both modalities were evaluated during the treatment period.

Adverse effects were evaluated during the treatment period. In addition to, follow up was done

every month for 4 months after the end of the treatment course to detect any recurrence of melasma.

STATISTICAL ANALYSIS

The collected data were analyzed by computer using Statistical Package of Social Services version 24 (SPSS). Suitable statistical tests of significance were used after checked for normality. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$). P-value < 0.001 was considered highly statistically significant (HS), and P-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

All patients completed the treatment course. No statistically significant differences were found between both groups as regards demographic or clinical data of all participants. The severity of melasma significantly decreased after 4 treatment sessions with triamcinolone injection. (Table 1).

The mean duration of melasma among the Triamcinolone group was (5.26 ± 4.79) years while it was (5.67 ± 4.2) years in Kligman' formula group with no significant difference between both groups. Half of the studied patients have mixed melasma in both Triamcinolone group and Kligman' formula group (54.5% vs 45.5%) respectively, and the most prominent melasma pattern was malar pattern in both groups (63.6% versus 59.1%) respectively. There were no significant differences between both groups regarding skin type, melasma type and melasma pattern.

According to (MASI) score melasma was mild (with MASI score from 1 to 16) in 59.1% and 50% in Triamcinolone group versus Kligman' formula group respectively, and moderate (with MASI score from >16 to 32) in 22.7% and 27.3% in Triamcinolone group versus Kligman' formula group respectively and severe (with MASI score from > 32 to 48) in 18.2% versus 22.7% in Triamcinolone group versus kligman' formula group respectively with no statistical significant difference between both groups regarding melasma severity (Table 1). In group 1(Triamcinolone injection), the mean of MASI after 3months (7.8 ± 8.11) was significantly less than the mean of MASI at baseline (15.38 ± 11.3). In group 2 (Kligman' formula), the mean of MASI after 3 months (7.57 ± 8.64) was significantly less than the mean of MASI at baseline (16 ± 12.92). MASI score significantly decreased all through treatment course in both groups (table 2, 3). After 3 months, the mean percent of decrease in MASI was 54.46 ± 21.62 in Triamcinolone group versus 57.86±19.75 in kligman group (Table 2,3).

The therapeutic response after 3 months of treatment was: good in 11 patients (50%) in Triamcinolone, versus 11 patients (50%) in Kligman' formula and medium in 7 patients (31.8%) in Triamcinolone, versus 8 patients (36.4%) in Kligman' formula and poor in 4 patients (18.2%) in Triamcinolone, versus 3 patients (13.6%) in Kligman' formula as shown in table 4.

Patient satisfaction

22.7% of patients treated with Triamcinolone injection were completely satisfied versus 36.4 % of kligman group. 36.4% of patients of both groups were greatly satisfied of results. 36.4% of Triamcinolone group versus 18.2 % of Kligman group were moderately satisfied. 4.6% of Triamcinolone versus 9.1 % of Kligman group were not satisfied. The difference between both groups regarding therapeutic response and patient satisfaction was not significant. The relationship between the therapeutic response and different clinical variables of patients in both groups wasn't significant (table 5).No side effects were reported with triamcinolone injection except for mild pain during injection, while Kligman's formula was associated with dermatitis, irritation, and burning sensation. Only 1 patient (4.5%) of Triamcinolone group showed recurrence of melasma versus 3 patients (13.6%) of kligman group during 4 months follow-up period.

Table (1): Demographic and clinical data of all patients:

Variable	Triamcinolone microinjection (n=22)		kligman' formula (n=22)		Chi-square test	p-value
Age: (year)						
Mean ± SD **Median (Range)**	37.05±6.41 35.5 (28-53)		37.86± 7.04 37 (23-58)		Mann Whitney 223.500	0.663 (NS)
Variable	(n=22)		(n=22)			P
Duration: (year)						
Mean ± SD **Median (Range)**	5.26 ± 4.79 3.5(0.08-20)		5.67 ± 4.2 5(0.75-17)		MW test 217.500	0.562 NS
Variable	No	%	No	%		P
Pregnancy:						

Variable	Triamcinolone microinjection (n=22)		kligman' formula (n=22)		Chi-square test	p-value
No	22	100.0	22	100.0	----	----
Yes	0	0.0	0	0.0		
Sun Exposure:						
No	0	0.0	0	0.0	----	----
Yes	22	100.0	22	100.0		
Family History:						
No	16	72.7	16	72.7	Fisher's	1.000
Yes	6	27.3	6	27.3		(NS)
Previous therapy:						
No	16	72.7	17	77.3	0.121	0.727
Yes	6	27.3	5	22.7		(NS)
Skin type:						
III	5	22.7	10	45.5	Fisher's	0.203
IV	17	77.3	12	54.5		(NS)
Melasma type:						
Epidermal	8	36.4	7	31.8	1.534	0.464
Dermal	2	9.1	5	22.7		(NS)
Mixed	12	54.5	10	45.5		
Pattern:						
Malar	14	63.6	13	59.1	0.370	0.931 (NS)
Facial	7	31.8	7	31.8		
Mandibular	1	4.5	2	9.1		
Severity:						
Mild	13	59.1	11	50.0		0.831
Moderate	5	22.7	6	27.3		(NS)
Severe	4	18.2	5	22.7		

Mann- Whitney test P < 0.05 is significant. NS: Not significant.
Fisher's Exact Test P > 0.05 is not significant.

Table (2): Changes of Melasma area severity index (MASI) among the studied Triamcinolone group through treatment period:

Melasma area severity index (MASI)	MASI at baseline	MASI after 1-month	MASI after 2-months	MASI after 3-months
Mean ± SD	15.38 ± 11.3	13.15 ± 11.21	9.23±8.82	7.8 ± 8.11
Median	12	8.1	4.2	3.45
Min-max	1.8-34.2	1.2-33.6	1.2-27	1.2-22.5
#P- value of Freidman test: 0.000*				
P-value Of Wilcoxon signed rank test ‡	Reference	0.001* (HS)	0.000* (HS)	0.000* (HS)
		Reference	0.000* (HS)	0.000* (HS)
			Reference	0.005* (HS)

Freidman test for comparison between all through follow up period
‡ Wilcoxon signed rank test for comparison between different timing
*significant P-value <0.05, HS=highly significant

Table (3): Changes of Melasma area severity index (MASI) among the studied Kligman' formula treated group through treatment period:

Melasma area severity index (MASI)	MASI at baseline	MASI after 1-month	MASI after 2-months	MASI after 3-months
Mean ± SD	16 ± 12.92	11.96 ± 10.35	9.6±9.7	7.57 ± 8.64
Median	15.3	8.7	5.4	3.9
Min-max	1.8-38.6	1.2-33.2	1.2-33.2	0.6-30.4

Melasma area severity index (MASI)	MASI at baseline	MASI after 1-month	MASI after 2-months	MASI after 3-months
#P- value of Freidman test: 0.000*				
P-value Of Wilcoxon signed rank test ‡	Reference	0.000* (HS)	0.000* (HS)	0.000* (HS)
		Reference	0.000* (HS)	0.000* (HS)
			Reference	0.000* (HS)

Freidman test for comparison between all groups
‡ Wilcoxon signed rank test for comparison between 2 groups
*significant P-value <0.05, HS=highly significant

Table (4): Therapeutic response among the studied groups:

Therapeutic response	Triamcinolone injection (N=22)		kligman' formula (N=22)		P- value
	No.	%	No.	%	
% of decrease in MASI					
Mean ± SD	54.46 ± 21.62		57.86±19.75		0.549 (NS)
Median (Range)	53.57(23.8-91.67)		61.9(16.17-87.5)		
Therapeutic response					
Poor	4	18.2	3	13.6	0.901 (NS)
Medium	7	31.8	8	36.4	
Good	11	50.0	11	50.0	

#Chi-square test
P > 0.05 is non-significant. NS: Not significant

Table (5): Patient satisfaction after treatment among the studied groups:

Item	Triamcinolone injection (N=22)		kligman' formula (N=22)		P- value
	No.	%	No.	%	
Patient satisfaction					
Not satisfied	1	4.6	2	9.1	0.501 (NS)
Moderately satisfied	8	36.4	4	18.2	
Greatly satisfied	8	36.4	8	36.4	
Completely satisfied	5	22.7	8	36.4	

Group (I): Intralesional triamcinolone.

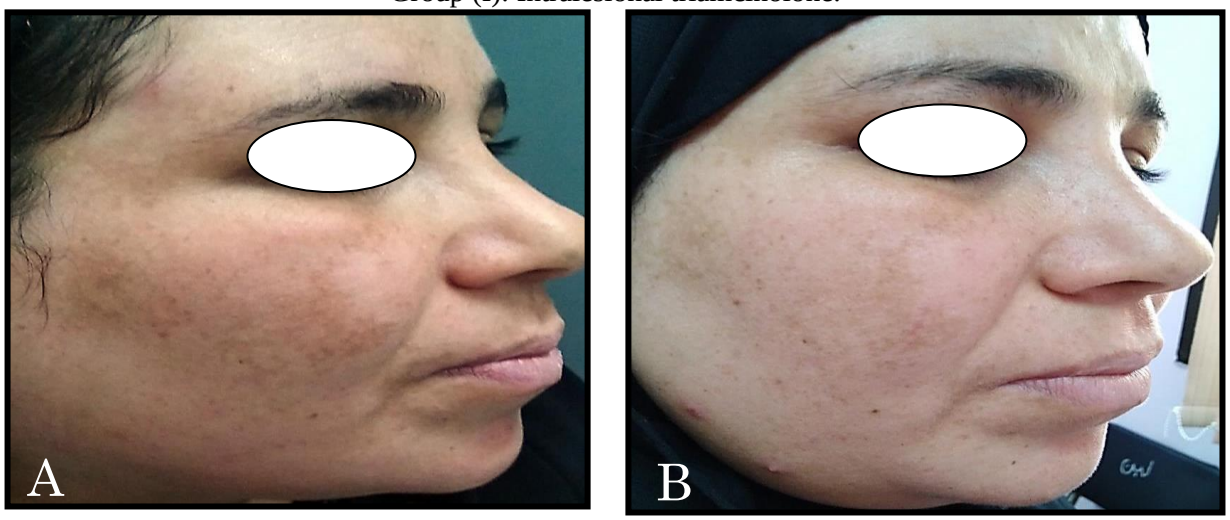

Figure (1): female patient with epidermal melasma excellent response. (a) at base line (b) after 3months of treatment.

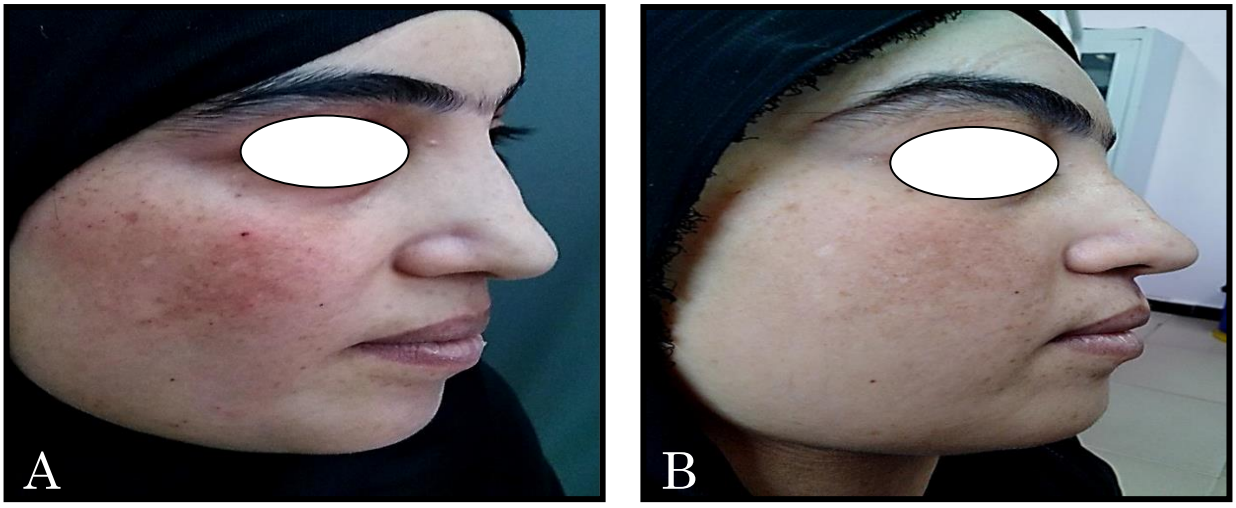

figure (2): female patient with mixed melasma showing good response. (a) at base line (b) after 3months of treatment.

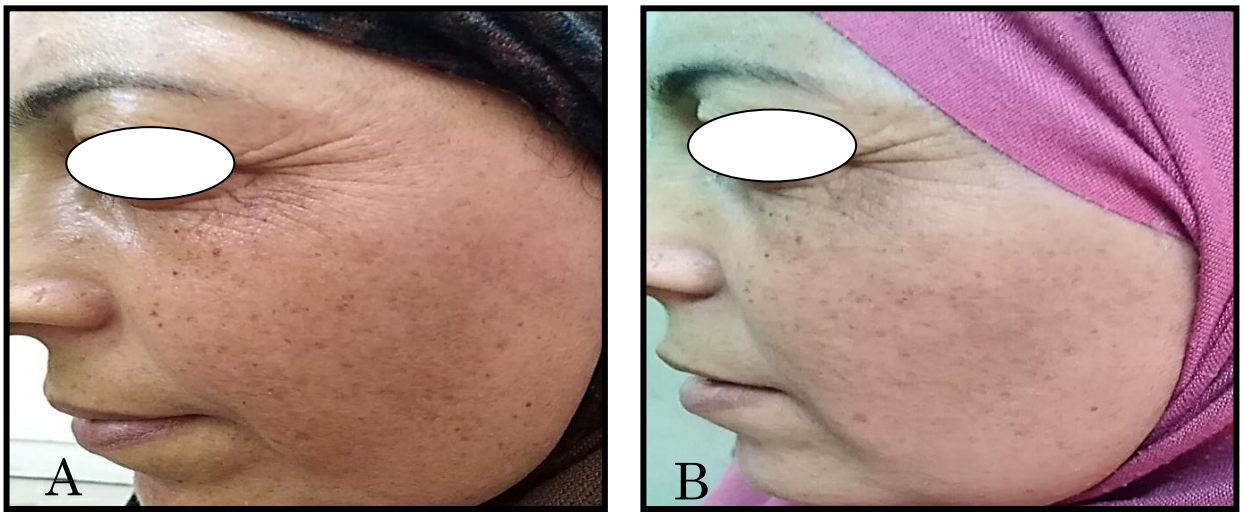

Figure (3): female patient with epidermal melasma showing good response. (a) at base line, (b) after 3months of treatment.

Group (II): Kligman formula

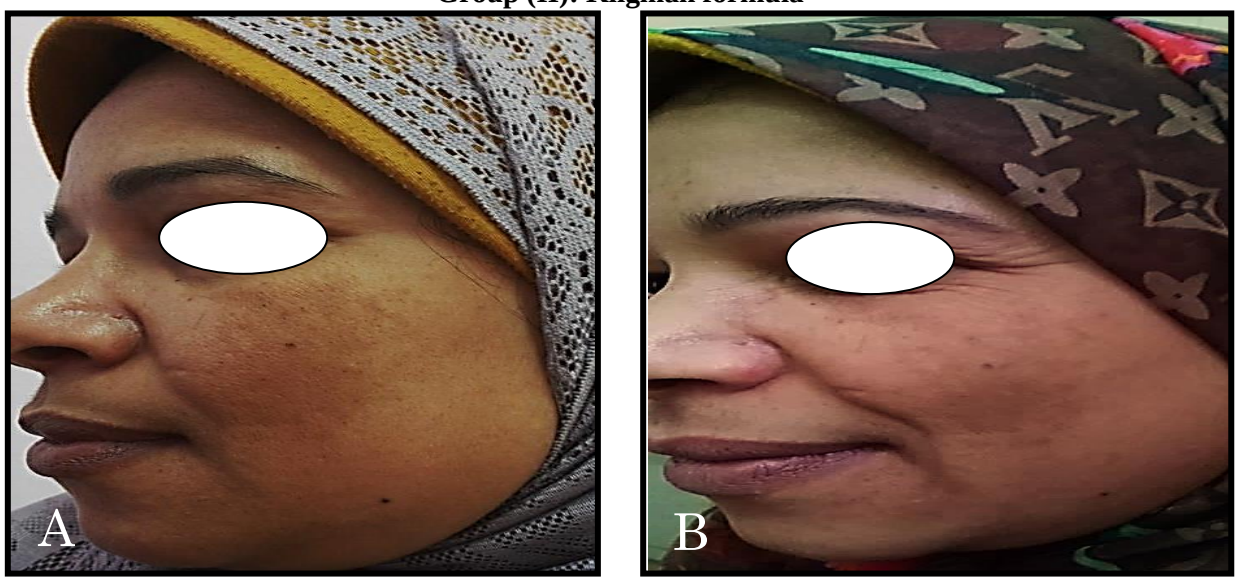

Figure (4): female patient with epidermal melasma showing good response. Treated with Kligman formula. (a) at base line, (b) after 3months of treatment.

Figure (5): female patient with epidermal melasma showing excellent response. Treated with Kligman formula. (a) at base line, (b) after 3months of treatment.

DISCUSSION

Melasma is a disorder of hyperpigmentation of excessive psychosocial distress. It is described as asymmetrical light brown to dark muddy brown macules and patches involving the face (i.e., cheek, forehead, nose, upper lip, and chin). The melasma pathogenesis is not clearly understood. Women with Fitzpatrick skin photo types III–V are more prone to get melasma. The most common factors include genetic tendency, pregnancy, oral contraceptives, endocrine disorders, hormonal therapy, drugs that contain phototoxic agents, and stress. Ultraviolet light appears to be a major triggering or aggravating factor for melasma [2].

The main target in the treatment of melasma is to inhibit the production and transfer of melanin aiming to restore the normal skin colour with the least complications. Topical treatment stills the main treatment modality of melasma. Although there are different topical treatment agents of melasma, its treatment is still challenging [4,6]. It is difficult to treat melasma, and the disorder may be intractable. Protection from Ultraviolet radiation (UV) rays, inhibition of melanocyte activity and melanin synthesis, and the disruption and removal of melanin granules are principles of therapy [7].This study showed significant reduction in the severity of melasma after four treatment sessions with intralesional triamcinolone injection, with no statistically significant difference in the therapeutic response between triamcinolone injection and Kligman' formula.

UV is the main triggering factor of melasma, in addition to, its stimulating effect on the melanogenic activity, chronic exposure to UV radiation stimulates the expression of matrix metalloproteinase (MMP)-2 and MMP-9 in the skin with subsequent degradation of extracellular matrix and disruption of the basement membrane [8]. The therapeutic effect of steroid on melasma might come from its inhibitory effect on the expression of different inflammatory mediators those are involved in the pathogenesis of melasma such as MMP2, MMP9, and IL1a, IL 1b, IL6, VEGF, PGF2, PGE2, and PGD2. Also, corticosteroid could inhibit melanogenesis in smaller melanocytes. In addition, steroid probably interfere with the formation of melanin in melanocytes which are small [6].

This study showed significant reduction in the severity of melasma after four treatment sessions with intralesional triamcinolone injection.

The results of this work came in agreement with Eshghi et al [6] who also stated highly melasma improvement after triamcinolone treatment.

Kligman's formula is the most popular combination therapy for melasma, so we selected it as a control group in this study. The effectiveness of Kligman formula has been proven by different previous studies (15,16,17). This came in agreement with the results of the present study that revealed significant reduction of the severity of melasma from 16 ± 12.92 to 7.57 ± 8.64 after treatment with Kligman's formula for 3 months. According to results of this study, the relationship between the therapeutic response and different clinical variables such as, type, severity, or duration of melasma in both groups wasn't statistically significant. Regarding intralesional triamcinolone, no side effects were reported except for mild tolerable pain at time of injection. These results came in agreement with Eshghi et al **[6]** who also stated that there were no side effects during melasma treatment by intralesional triamcinolone**.** On the other hand, side effects, including irritation,

dermatitis and burning were detected in patients treated with Kligman's formula. This came in agreement with the previous studies which reported the side effects of Kligman's formula such as skin irritation, erythema, burning sensation and desquamation [9].

The absence of side effects in patients treated with low concentration of intralesional triamcinolone could be an important advantage of intralesional triamcinolone over Kligman's formula that is frequently associated with the previously mentioned side effects.

One patient (4.5%) of the triamcinolone group and 3 patients (13.6%) of Kligman group showed recurrence of melasma during the 4-months follow-up period. The low recurrence rate associated with triamcinolone therapy is an important advantage in addition to its efficacy and lower incidence of side.The results of this study indicate that intralesional triamcinolone might decrease the rate of melasma recurrence**.**

CONCLUSION

This study concluded that intralesional triamcinolone in low concentration could be an alternative simple, economic and safe treatment modality for melasma. However, further studies are still needed to confirm these results and to reach the most effective and safe concentration of triamcinolone injection therapy for melasma.

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