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Comparative Study between the Efficacy of Intradermal Injection and Oral Administration of Tranexamic Acid in Treatment of Melasma

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Abstract

Melasma is an acquired hypermelanosis characterized by light to dark-brown macules and patches on sun-exposed areas. Most cases of melasma occur in women in the reproductive age with darker skin types, but all ages, races, and skin colours may be affected, Tranexamic acid is an antiplasminogen agent with well-documented efficacy against melasma. comparison of the efficacy and safety of intradermal injection and systemic administration of tranexamic acid in treatment of melasma. 40 female patients complaining of melasma were divided randomly into two groups, group A and B. mMASI score before and after treatment did not differ significantly between both groups . The response to the treatment was best in group A who was received intradermal injection(4mg/ml)TXA, followed by group B who was received oral TXA in a dose of 250 mg twice daily for 3 months. In group A, there was excellent response was detected in 6 patients (30%), good response was detected in 6 patients (30%), moderat response was detected in 5 patients (20%), mild response was detected in 1 patient (5%) and no response was detected in 2 patient (10%). In group B, excellent response was detected in 0 patients (0%) good response was detected in 1 patients (5%), moderat response was detected in 12 patients (60%), mild response was detected in 3 patient (15%) and no response was detected in 4patient (20%). Tranexamic acid may be a new treatment option for melasma. It is a safe, well-tolerated and effective treatment method.

1. Introduction

Melasma is an acquired pigmentary disrder classically manifesting as hyperpigmented macules and patches distributed on the face,neck and rarely the upper limbs.most cases of melasma occur in women in reproductive age with darker skin tones,but all ages,races and skin colours may be affected [1].

Melasma has a significant impact on appearance, causing psychosocial and emotional distress,and reducing the quality of life of the affected patient [1].

Different therapeutic modalities, especially the gold standard hydrquinone have been used in treatment of melasma.the existing other modalities which are used includ retinoic acid ,kojic acid ,azelaic acid ,peeling agents like glycolic,trichloroacetic acid ,salicylic and lactic acid. Physical agents like lasers and dermabrasion have also been tried.However,the disorder is difficult to treat,particularly in dark-skinned individuals [2].

Newer formulations that are being tried include tranexamic acid (TA), rucinol (4-n-butylresorcinol), oligopeptides, slymarin and orchid extracts. [3]

Tranexamic Acid (TA) can be used orally topically or by intradermal microinjection . TA can interfere with the catalytic reaction of tyrosinase and inhibit melanogenesis. It inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes. This results in less free arachidonic acid and a diminished ability to produce prostaglandins, and this decreases melanocyte tyrosinase activity. [3]

The present study aimed at comparison of the efficacy and safety of intradermal injection and systemic administration of tranexamic acid in treatment of melasma.

2. Patients and methods

This cross sectional study population included forty patients complaining of melasma, They were selected from patients attending the Dermatology, Venerology and Andrology clinic, Benha University Hospital. This study was conducted from June 2016 to June 2017.

The present study was approved by the local ethics committee on research involving human subjects of Benha Faculty of Medicine. Informed consents were obtained from each individual before being enrolled in the study.

Inclusion Criteria

Females between 18 and 50 years of age with moderate-to-severe bilaterally symmetrical distribution of melasma with photoskin type III-IV-Vwere included in the study .

Exclusion criteria

1. Patients on hormone replacement therapy or oral contraceptives,
2. Pregnancy and lactation.
3. History of bleeding disorders, concomitant use of anticoagulants.
4. Any known drug allergy especially to the study drug.
5. Associated medical illnesses.
6. History of any other depigmenting treatment in the past month.
7. Active herpes simplex.
8. Facial warts or active dermatoses.

The current study included 40 femal patients complaining of melasma . They were divided randomly into two groups, group A and B. The baseline parameters (age, cause,distribution of melasma) between the two groups and other clinical data were statistically comparable.

2.1 Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY:

IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics:Mean, Standard deviation (± SD) for parametric numerical data. Frequency and percentage of non-numerical data. Analytical statistics: Student T Test was used to assess the statistical significance of the difference between two study group means. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. p is significant if ≤0.05 at confidence interval 95%.

3. Results

A randomized controlled clinical trial was conducted, 63 cases of hyperpigmentation were assessed for illegibility; 23 were excluded. All 40 participants completed the study; patients were divided into two groups; 20 were treated by oral and 20 were treated by ID tranexamic acid. They were followed up for 6 months, none of them was missed follow up.

The present study included 40 female patients suffered from melasma; 20 patients were treated with intradermal injection of tranexamic acid solution; and 20 patients were treated with oral tranexamic acid.

Mean age of studied patients was 42.3 years; 6 cases were skin type III (15%), 32 were type IV (80%) and 2 were type V (5%). About one third of cases were positive family history of melasma (32.5%). Most cases had malar pattern (97.5%), while centrofacial was present in 57.5%. Using wood's light, revealed epidermal type in 42.5% and mixed type in 57.5% of all cases. Table 1. Mean mMASI score before treatment was 7.1, while that after treatment was 3.9. Fig(1)

Table (1) Age, skin type, family history,disease duration and clinical features of all studied patients.

			Melasma N=40	
Age (years)		Mean, SD	42.3	5.9
Fitzpatrick skin type	**III**	N, %	6	15
	IV	N, %	32	80
	V	N, %	2	5
Family history		N, %	13	32.5
Disease duration (year)		Mean,SD	4.4	1.3
Pattern of melasma	**Malar**	N, %	39	97.5
	Centrofacial	N, %	23	57.5
Wood's light ex	**Epidermal**	N, %	17	42.5
	Mixed	N, %	23	57.5

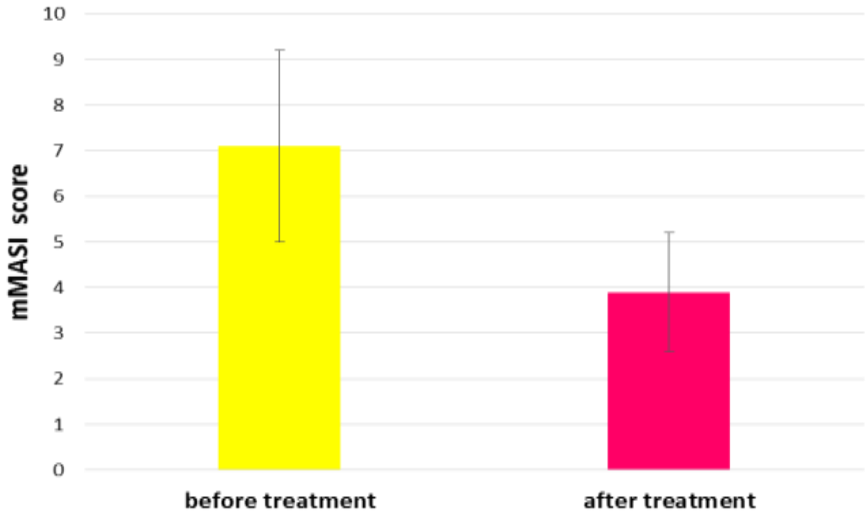

Fig (1) mMASI before and after treatment in all studied cases.

Clinical improvement was evaluated using a quartile grading scale as follows; 0=no improvement, 1=mild (<25%), 2 =moderate (26-50%), 3=good (51-75%) and 4=excellent (percent improvement, > 76%).Mean response to treatment (improvement) was 41.3%. No response was observed in 15%, mild in 10%, moderate in 42.5%, good in 17.5% and excellent response in 15% of all studied cases Table(2).

Table (3) Response to treatment in all studied cases.

		Melasma N=40	
Response to treatment (%)	Mean, SD	41.3	13.1
No	N, %	6	15
Mild (<25%)	N, %	4	10
Moderate (26-50%)	N, %	17	42.5
Good (51-75%)	N, %	7	17.5
Excellent (>76%)	N, %	6	15

mMASI score before and after treatment did not differ significantly between both groups. Table (3) ID route showed significant improvement when compared to oral route Table (4).

Table (3) Comparison of mMASI before and after treatment between all studied groups.

	Oral tranexamic acid N=20		ID tranexamic acid N=20		p
	mean	**SD**	**mean**	**SD**	
mMASI before treatment	69.1	17.7	71.9	13.6	0.799
mMASI after treatment	47.3	15.4	32.3	10.6	0.056*

Numerical data were compared using t test.

Table (4) Comparison of response to treatment between all studied groups.

		Oral tranexamic acid N=20		ID tranexamic acid N=20		p
Response to treatment (%)	**Mean, SD**	28.5	9.1	54.6	17.9	0.001*
No	**N, %**	4	20	2	10	0.005*
mild (<25%)	**N, %**	3	15	1	5	
moderate (26-50%)	**N, %**	12	60	5	25	
good (51-75%)	**N, %**	1	5	6	30	
excellent (>76%)	**N, %**	0	0	6	30	

Numerical data were compared using t test; categorical data were compared sing chi square test.

4. Discussion

In our study, there were two groups.Group(A) included 20 patients were treated with intradermal injection of TXA. After gentle cleansing with alcohol, a topical anesthetic cream was applied under an occlusive dressing for 1 hour. 0.05 ml of tranexamic acid solution in normal saline (4mg/ml) into the melasma lesion at 1 cm interval by using sterile insulin syringe, every 2 weeks for 12 weeks (Lee et al. ,2006).And group(B) included 20 patients were treated with oral tranexamic acid in a dose of 250 mg twice daily for 3 months [4].

Regarding the efficacy of treatment in the present study, group A who was received intradermal injection showed the highest efficacy, followed by group B who was received oral TXA.

In group A, there was significant decrease in P value(<0.001*) and mMASI score from the base line to the end of the treatment. These results were in agreement with [5] who used intradermal injection of 0.05 ml of tranexamic acid 4mg/ml in patients with melasma weekly for 12 weeks .Also, [6] who compared microinjections of tranexamic acid (4mg/ml) and tranexamic acid with microneedling in patients with melasma three times at monthly intervals.there was improvement in MASI score in both groups but with no significant difference in the mean MASI scores between the two groups.

In group B, there was significant decrease in Pvalue(<0.001*) and m MASI score from the base line to the end of the treatment but less than those in group A. These results agreed with [7] who studied the role of oral tranexamic acid in a dose of 250 mg twice daily for 3 months in treatment of melsma.

We obtained good results by both modalities as mMASI score before and after treatment did not differ significantly between both groups . This was in agreement with [8] who stated that the mean percentage reduction in MASI was comparable in both groups at each visit; any differences were not statistically significant, suggesting that the efficacy of TXA is perhaps independent of its route of administration.

Regarding the response to the treatment of melasma in the present study, the best response was in group A followed by group B.

In group A, an excellent response was detected in 6 patients (30%), good response was detected in 6 patients (30%), moderat response was detected in 5 patients (20%), mild response was detected in 1 patient (5%) and no response was detected in 2 patient (10%). These results were in agreement with Lee et al., (2006) who stated that at the end of treatment there was very good response in (9.4%), good response was detected in (76.5%) and poor response was detected in (14.1%).

In group B, excellent response was detected in 0 patients (0%) good response was detected in 1 patients (5%), moderat response was detected in 12 patients (60%), mild response was detected in 3 patient (15%) and no response was detected in 4 patient (20%). These results were in agreement with [4] who studied the effect of oral administration of 250 mg of tranexamic acid twice daily for 6 months in the treatment of melasma in 74 patients revealed that, there was excellent response in (10.8 %), very good response in (54 %), good response in (31.1 %) and poor response in (4.1 %). Aamir and Naseem [9] who performed a cross sectional study of 65 patients given 250 mg oral TA twice a day for 6 months the total improvement rate was found among 98.5% of the subjects (23% excellent, 63% good, and 12% fair).Also [5] studied the effect of oral administration of 250 mg of tranexamic acid twice daily in 561 patients for 4 months In terms of treatment response, 89.7% of patients had documented improvement, 10% remained unchanged, and 0.4% worsened.

While some studies had used higher doses (750–1500 mg/day) than those used in our study as [10]. Another studies found that it's better to prolonge the prescription period than increase the dosage of TXA to avoid more side effects [4], [8]

But this response was in disagreement with [8] there study was completed by 39 patients group (A) received oral TA and 41 patients group (B) received intradermal injection of TA. Very good response was seen in 25(64.1%)patients and good response was seen in14(35,9%) in groups A. while in group B very good response was seen in 9 (22%) and good response in 32 (78.0%) patients.and also [11] who had two groups of patients, 32 received oral TA and 32 patients received intradermal injection of TA and found that all the 32 patients in the oral group (100%) showed >50% improvement, of which 8 showed >75% improvement. In the intralesional group, 17 (53%) patients had >50% improvement, 3 of whom had >75% improvement. The remaining 15 patients in this group had <50% improvement. Thus, the oral group showed significantly better response as compared to the intralesional group.

This difference may due to different time interval, number of injection sessions as [8] and [11] injected it every four weeks for maximum 4 cycles,while in our study the injection was every 2 weeks for maximum 6 cycles.and our study was limited by the small number of patients(40)while thier studies enrolled in 80 and 64 patients respectively.And patients skin type in thier studies were IV and V while in our study was III,IV and V.All patient enrolled in our study were females while in thier studies included males and females with melasma as this indecate the effect of hormones in the results and the effect of genetic factor.

Regarding the side effects in our study, they were more reported in group A while no side effects were reported in group B.ingroup A, there was burning pain in all patients (100%) and erythema in 4 patients (20%). These results in agreement with [5] and [11] they reported that there were burning pain and wheal at the site of injection in all patients (100%). While in the study conducted by [8] showed that there was pain and transient oedema,in 13 patients out of 41 (26%) . In group B, no side effects were reported in all patients. While [4] , [8] and [11] reported that there were mild epigastric discomfort and hypomenorrhea in afew number of patients. In addition to these skin rashes due to allergy as well as dizziness, alopecia, drowsiness, and hyposexuality were reported by [4] and deep vein thrombosis was reported by Lee et al., [12].

5. Conclusion

Tranexamic acid may be a new treatment option for melasma. It is a safe, well-tolerated and effective treatment method . We obtained good results by both modalities but the response was better with intrademal injection of TXA than oral administration. Also, its efficacy in treatment of melasma requires further evaluation in larger clinical trials.

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