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Original Article

Effectiveness of intra-lesional tranexamic acid in treatment of melasma

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Abstract

Introduction Melasma is acquired hypermelanosis of skin. It mostly occurs on face involving the cheeks, temple and upper lip. Especially it is seen in people living in areas with intense ultraviolet radiations. It occurs mostly in ladies of childbearing age. The condition may likewise occur in men. This condition is increasingly common in women accounting for 90% of all cases.

Objective The objective of this particular study is to determine the effectiveness of intralesional tranexamic acid in the treatment of melasma.

Methods This Quasi-experimental study was carried out in Dermatology Department of Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore from February 2018 to February 2019. One hundred seventy patients were enrolled for this study.

Results The mean age of patients was 35.46±8.00 years. Out of 170 patients, 66 (39%) were males and 104 (61%) were females. Thus the female to male ratio was 1.57:1. The improvement after four weeks of treatment, 11 (7.0%) patients had excellent improvement and most of the patients i.e. 84 (49.0%) had good improvement, 66 (39.0%) had fair and 9 (5.0%) had poor response. After 8 weeks, 52 (31.0%) patients had excellent response, majority of patients 93 (55.0%) had good improvement, 21 (12.0%) had fair and 4 (2.0%) had poor improvement. The improvement after 12 weeks of treatment showed that 71 (41.8%) had excellent improvement, 67 (39.4%) had good, 30 (17.6%) had fair improvement and only 2 (1.2%) had poor improvement. The comparison of effectiveness after treatment of 4 and 8 weeks of treatment which is statistically significant $p < 0.05$. The comparison for effectiveness after treatment of 4 and 12 weeks which is statistically significant $p < 0.05$.The comparison of effectiveness after treatment for 8 and 12 weeks which is statistically not significant p 0.06.

Conclusion We conclude that intralesional microinjection of TA appears to be a potentially new and promising therapeutic tool that can be easily performed in outpatient settings, and this treatment produces relatively rapid results without significant side effects. For this reason, it may be used as part of melasma treatments, especially for the dermal and mixed melasma. Larger studies will be needed to determine the optimal dosage, the injection frequency, the injection technique, long term benefits, and any potentially additional adverse effects.

Key words
Melasma, intralesional tranexamic acid.

Introduction

An attained hypermelanosis is called melasma. It usually presents with irregular patches of brown colour and macules, symmetrically distributed in area of body that is exposed to sun and facial area like nose, cheeks, forehead, lips, and forearms.[1] This ailment is predominantly found in women who are in the childbearing years and approximately 90% cases are reported in women, belonged to the regions of Africa,

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Hispania, Asia, or Middle East. According to Lynde, *et al.*[2] it is more common in women. Men represent only 10% of cases. Though the Melasma's pervasiveness in women of Asia is not completely identified but the estimation is that it is high up to 40% among women and in men it is up to 20%. The terms Melasma or Chloasma are usually mentioned interchangeably, that is hyperpigmentation which mostly occurs because of imbalance in pregnancy or ovarian hormones.[3]

On the basis of histopathology, three types of Melasma are there: Dermal Melasma, which exists with color of greyish blue and faded margin. Second type is Epidermal Melasma, which has well margined border and it appears in brown color and the third one is indeterminate or mixed Melasma. Dermal type of Melasma has epidermal hyperpigmentation and dermal melanophages. Epidermal type of Melasma has basilar layer's hypermelanosis. Na *et al.*[4] have found that a traditional hemostatic drug, tranexamic acid (TA), has hypopigmentory effect on Melasma lesions and it also prevents UV-induced pigmentation.

According to the study of Ando *et al.*[5] the intracellular release of arachidonic acid (AA), an antecedent of prostanoid, and the dimension of alphamelanocyte-stimlating hormone increment as the aftereffect of plasmin activity. These two substances can impel melanin synthesis. In this manner, the anti-plasmin movement of TA is thought as the fundamental component of hypopigmentory impact of this agent. In a very recent study, a significant decrease in epidermal pigmentation and reversion of Melasma-related dermal changes were seen after using both topical and intralesional TA for 8 weeks.[4]

Materials and Methods

The Quasi-experimental design was done in the Department of Dermatology at Shaikh Zayed Hospial, Lahore from February 2018 to February 2019. A total of 170 patients of Melasma fulfilling the criteria, presenting in Out-patients Department of Dermatology were included in the study. Informed consent was taken before enrollment. Information was collected in the form of questionnaire that included age and sex. Grading of type of melasma was done with wood's lamp examination. After applying local anesthesia, 0.05ml Tranexamic acid (4mg/ml) was injected intradermally into melasma lesion at 1cm interval by using a 0.5ml insulin syringe with a 30 gauge needle. This was repeated at 4, 8 and 12 weeks. Before and after treatment pictures were taken and patient was asked to use sunblock. Responses were evaluated on the basis of Melasma Area & Severity Index (MASI) score. It was calculated in the start of therapy (baseline) and at the end of 4, 8 and 12 week. Quantitative variables such as age of patients were considered as mean and standard deviation. Qualitative variables such as gender of patient and efficacy were expressed in terms of frequencies and percentages. The category of improvement was assessed by McNemar Test at each visit and at the end of treatment. P value ≤ 0.05 was considered statistically significant.

Inclusion Criteria

Clinically diagnosed cases of melasma, Age range - 20-50 years, both genders and subjects with normal Ferritin & TSH level.

Exclusion Criteria

Prior known allergic response to tranexamic acid, Atopic patients, Pregnancy, Lactation, Patients taking oral contraceptive pills (OCPs), Acute febrile illness, Subjects who have received any treatment for melasma in the last month before enrollment and Immuno-suppression/ HIV infection.

Results

Total of one hundred seventy patients were selected for this study. The age range was 20 to 50 years. The mean age of patients was 35.46±8.00 years **(Table 1)**. Out of 170 patients, 66 (39%) were males and 104 (61%) were females. Thus the female to male ratio was 1.57:1 **(Table 2)**. **Table 3** shows the improvement after four weeks of treatment. 11 (7.0%) patients had excellent improvement and most of the patients i.e. 84 (49.0%) had good improvement, 66 (39.0%) had fair and 9 (5.0%) had poor improvement. After 8 weeks, 52 (31.0%) patients had excellent response, majority of patients 93 (55.0%) had good improvement, 21 (12.0%) had fair and 4 (2.0%) had poor improvement **(Table 4)**. The improvement after 12 weeks of treatment showed majority of patients i.e. 71 (41.8%) had excellent improvement, 67 (39.4%) had good, 30 (17.6%) had fair improvement and only 2 (1.2%) had poor improvement **(Table 5)**. **Table 6** shows the comparison of effectiveness after treatment of 4 and 8 weeks of treatment which is statistically significant p <0.05. **Table 7** shows the comparison for effectiveness after treatment of 4 and 12 weeks which is statistically significant p <0.05. The comparison of effectiveness after treatment for 8 and 12 weeks which is statistically not significant p 0.06 **(Table 8)**. **Table 9** shows MASI score.

Table 1 Age Distribution of patients.

Age in years	*No.*	*%age*
20-30	66	39.0
31–40	49	29.0
41-50	55	32.0
Mean±SD	35.46±8.00	

Table 2 Sex distribution of patients.

Sex	*No.*	*%age*
Male	66	39.0
Female	104	61.0
F to M ratio	1.57:1	

Table 3 Frequency of improvement after 4 weeks.

Improvement	*No.*	*%*
Excellent	11	7.0
Good	84	49.0
Fair	66	39.0
Poor	9	5.0

Table 4 Frequency of Improvement after 8th weeks.

Improvement	*No.*	*Percentage*
Excellent	52	31.0
Good	93	55.0
Fair	21	12.0
Poor	4	2.0

Table 5 Frequency of Improvement after 12th weeks.

Improvement	*No.*	*Percentage*
Excellent	71	41.8
Good	67	39.4
Fair	30	17.6
Poor	2	1.2

Table 6 Comparison of Improvement between 4 to 8 weeks.

	4 weeks		*8 weeks*	
	No.	*%*	*No.*	*%*
Excellent	11	7.0	52	31.0
Good	84	49.0	93	55.0
Fair	66	39.0	21	12.0
Poor	9	5.0	4	2.0

Table 7 Comparison of improvement between 4 and 12 weeks.

	4 weeks		*12 weeks*	
	No.	*%*	*No.*	*%*
Excellent	11	7.0	71	41.8
Good	84	49.0	67	39.4
Fair	66	39.0	30	17.6
Poor	9	5.0	2	1.2

Table 8 Comparison of improvement between 8 and 12 weeks.

	8 weeks		*12 weeks*	
	No.	*%*	*No.*	*%*
Excellent	52	31.0	71	41.8
Good	93	55.0	67	39.4
Fair	21	12.0	30	17.6
Poor	4	2.0	2	1.2

Table 9 MASI score.

	MASI score	*P value*
Week 0	2.73±1.07	
Week 4	2.16±1.07	0.061
Week 8	1.74±0.94	0.007
Week 12	1.17±0.82	0.002

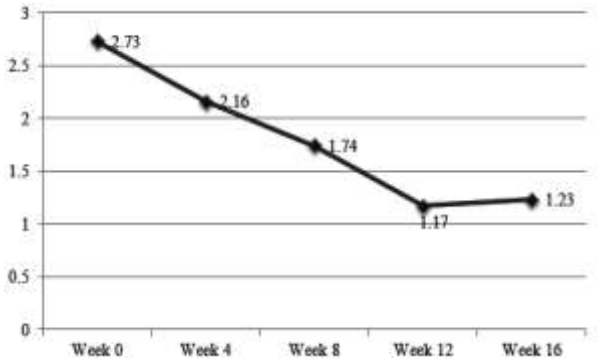

Figure 1 The modified MASI score before and after treatment.

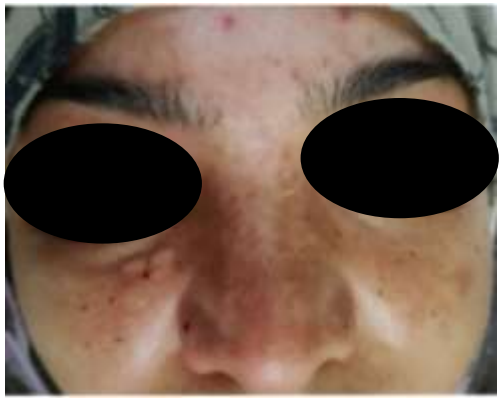

Figure 2A Before treatment.

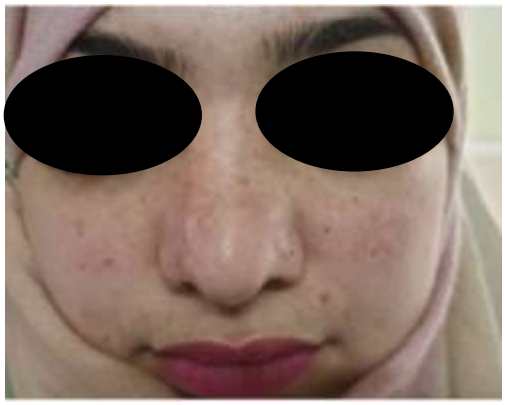

Figure 2B After 4 weeks of treatment results with intralesional tranexamic acid.

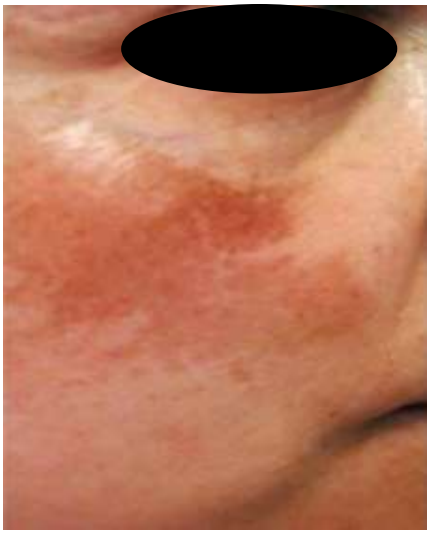

Figure 3A Before treatment.

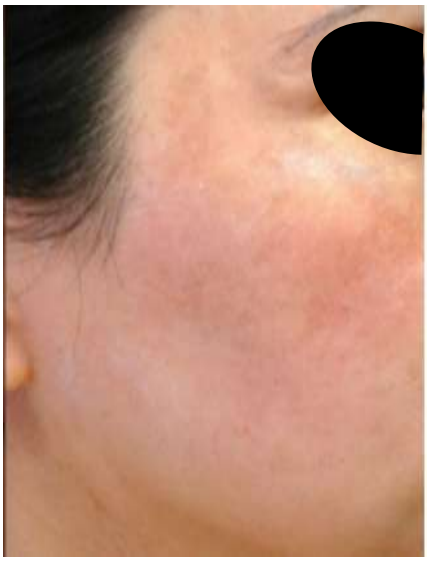

Figure 3B Patient after 12 weeks of treatment.

Discussion

Melasma is very common pigmentary disorder characterized by brown or grey patch which usually affects sun exposed skin mainly face, nose, forehead and chin. Studies have shown that melasma causes cosmetic disfigurement and leads to psychosocial distress. Even though Hydroquinone has been regarded as a gold standard for treatment of melasma, many other topical treatment options may include Retinoids, Kojic acid AHA, Ascorbic acid either alone or in combination. However local application of antipigmentary agents may cause irritant dermatitis, exogenous ochronosis and poor compliance may be an issue. Another obstacle in treating melasma is its bearings whether dermal or mixed type in which they are not very useful.

This has led dermatologists to more innovative, efficient and safer treatment modalities and among one of them is Tranexamic acid. There are studies which revealed that tranexamic acid (TA) is a plasmin inhibitor. It is a lysine analog and works by reversibly blocking lysine binding sites on plasminogen molecules, which ultimately results in decreased melanocyte activity. Many studies discussed the use of topical and oral tranexamic acid in melasma treatment. The outcome of the topical treatment is still not satisfactory while the oral tranexamic acid is quite dangerous due to the systemic side effects of the drugs when given in high dosage and taken for long durations. Recently, there has been growing interest in clinical trial studies using localized intradermal microinjection of tranexamic acid (TA). The goal of this treatment is to inject an adequate amount of medication directly to the problem point and avoid oral medication. Therefore, the study aims to evaluate the efficacy and side effect of intradermal microinjection of 4mg/ml of TA for treatment of melasma.

In this study, the age range of the patients was 20-50 years with mean age of 35.46±8.00. Most of the patients were between 20-30 years of age. In a similar study done by Qazi *et al.*[6] the most common age group was between 30-39 years (47.1%) and the mean age of patients was 30.1 years which is comparable with current study. In another study reported by Singh *et al.*[7] the mean age of melasma patients was 28.6±5.01 years which is comparable with our study.

In our study, 66 (39%) were male patients and 104 (61%) were female patients. Thus the female to male ratio is 1.57:1. This study revealed that most of the female patients (>50%) developed melasma between the second and fourth decades of life (20 to 35 years of age). In a study done by Martin *et al.*[8] 72% patients were females and males constituted 28% and female to male ratio was 2.57:1 which is comparable with our study. Another similar study conducted by Acher *et al.* found that female to male ratio of 3.28:1 and 4:1 respectively (Pawar *et al.*[9] 2015; Acher *et al.*[10] 2011).

In our study we injected 0.05ml (4mg/ml) of tranexamic acid intradermaly in melasma lesion at 1cm interval with a 30 guage needle after topical anesthetic application. Improvement was assessed at 4, 8 and 12 weeks using MASI score. After completion of study, MASI score in the 12th week significantly decreased compared to the baseline. For the mean modified MASI score after treatment a decrease was shown from 2.73±1.07 at baseline to 2.16±1.07, 1.74±0.94 and 1.17±0.82 at weeks 4th, 8th & 12th respectively. Changes in the MASI score slightly decreased since week 4th and showed statistically significant difference at week 8th ($p < 0.05$).

According to Perper *et al.*[11] and Kim *et al.*[12] Tranexamic acid was indicated to be a choice in treatment of melasma. However, there are scant studies that have assessed intradermal microinjection of TA as an effective and safe method. Previous studies had some disadvantages, mainly including lack of a control group.

Lee *et al.*[13] during a prospective study, investigated the effect of localized TA intradermal microinjection (4 mg/mL) on 100 women with melasma. About 85 patients completed the study, and a statistically significant decrease was observed in MASI at 8 and 12 weeks. In another study in 2009, Steiner *et al.* compared the effects of topical TA 3% with intradermal injection of TA (4 mg/mL) in 18 women with melasma. Group A used 3% TA twice a day and injection with TA (4 mg/mL) weekly for 12 weeks was performed for group B. Seventeen patients completed the study.

According to MASI score and calorimetric evaluation, both groups improved significantly and no significant difference was observed between them.

During a prospective study, Budamakuntla *et al.*[14] divided 60 patients into two groups. A group was under TA microinjection (4mg/mL) and another group under TA microneedling (4mg/mL) for 3 months (0, 4 and and followed-up for 3 months. In the microinjection group, 35.72% improvement was observed in MASI score, compared with 44.41% in the microneedling. Improvement in the microneedling group was better than the microinjection group. Elfar[16] and El-Maghraby in their study, treated 60 women in different ways to compare the effects of intradermal injection of TA (20 subjects) and silymarin cream as a strong antioxidant (20 subjects) and 50% glycolic acid peeling (20 subjects). TA (4 mg/mL) was injected intradermally at intervals of 1cm weekly for 12 weeks. Intradermal injection of tranexamic acid significantly reduced the MASI score from the baseline, but its effect was less than the silymarin cream and glycolic acid peeling. Sharma *et al.* during a study, investigated 100 patients (92 women and eight men) and divided them into two groups. One group was treated with oral 250 mg tranexamic acid twice a day and the other group was injected intradermally with TA 4mg/mL every 4 weeks. The treatment period was 3 months. Mean reduction of MASI in the 12th week was 77.96 in the oral group and 79.00 in the injection group, so no significant.

In another prospective comparative study in 2018, Shetty[17] and Shetty divided 40 patients into two groups. Group A were treated with intradermal injection of TA (4 mg/mL) once at 3 week intervals (0, 3, 6, 9 and 12 weeks) for 12 weeks and group B were treated with oral TA 250 mg twice a day for 12 weeks. According to MASI score reduction, difference was observed between them. Intradermal injection of TA has a higher clinical improvement (35.6%) compared to oral TA (21.7%).

The limitations of this study were the small number of participants, lack of blindness for the investigator, the inadequate duration of treatment and follow-up, and use of the MASI score, which is a subjective assessment method. We suggest organizing studies to accentuate the optimum dose and duration of treatment with intradermal TA injection alone or in combination with other lightening agents.

Conclusion

We conclude that intralesional microinjection of TA appears to be a potentially new and promising therapeutic tool in the treatment of melasma that can be easily performed in outpatient settings, and this treatment produces relatively rapid results without significant side effects.

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