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Original Article

Efficacy of intradermal tranexamic acid in melasma

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Abstract

Objective To determine the efficacy of intradermal tranexamic acid (TA) in the patients of melasma.

Methods This study was conducted in Dermatology OPD, Punjab Rangers Teaching Hospital over a period of 4 months from 14-08-2022 to 14-12-2022. A total number of 32 patients of melasma were enrolled after informed written consent. 2mL of concentrated tranexamic acid (50mg/ml) was injected intradermally, 1 ml on either side of face 1cm apart over the affected area. A total of 4 sessions were carried out, followed after every 2 weeks. Results were interpreted on the basis of MASI scoring before, during and after completion of the sessions. A mild topical steroid application was advised for 2 days. Sunscreen application was essentially prescribed.

Results Out of 32 enrolled patients of melasma, 56% showed 61-100% reduction in MASI scoring, which constituted a majority.

Conclusion We concluded that un-diluted intra dermal tranexamic acid is an excellent treatment modality for treatment of melasma without any side effects.

Key words
Melasma; Tranexamic acid (TA); Intradermal microinjections.

Introduction

Melasma is an acquired skin condition of pigmentary disorder marked by irregular pigmented patches and mostly occurs in females living in areas of intense ultraviolet (UV) light exposure. It is characterized by patchy pigmentation usually on sun exposed areas, especially on face, particularly in middle aged men and woman.[1]

The exact etiology of this disease and pathogenesis of melasma is not yet clearly defined; however, some etiological factors have been identified, including genetic background, pregnancy, hormonal therapies, and sun exposure.[2] Melasma has a significant psychological effect on the affected patients because of its disfiguring nature. Several treatment modalities are available for melasma such as topical use of bleaching agents like hydroquinone and hydrocortisone and chemical peeling etc.[3] However, these treatments can yield adverse effects such as contact dermatitis, mottled hypopigmentation, irritation, acneiform eruptions, and rebound hyperpigmentation.[4] Tranexamic acid is a derivative of amino acid lysine. It binds to the 5-lysine binding sites on plasminogen and inhibits the plasmin formation, displaces plasminogen from fibrin. The hypopigmentation effect is due to its antiplasmin activity, with a structural similarity relative to tyrosine.[5] The amount of TA used to treat

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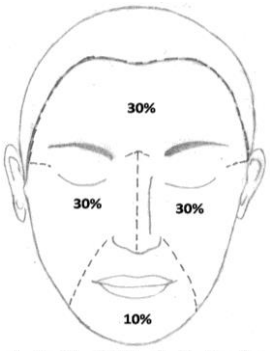
melasma is much less than the amount required for its antifibrinolytics effects. Transdermal injections have become a popular drug delivery route in recent years.[6]

Methods

A Prospective study was carried out in the outpatient department of Punjab Rangers Teaching Hospital Lahore for a period of 4 months starting from 14-08-2022 to 14-12-2022. A total of 32 (male and female) melasma patients aged 25 to 50 years were enrolled. Inclusion criteria was to include all patients 18 years and above with clinical signs of melasma. Patients with gynaecological, bleeding or clotting disorders, dermatological or systemic comorbidities, pregnant females and patients on topical therapy for melasma were excluded from the study. On the first visit, an informed consent was taken along with the demographic data of the patients. MASI (melasma area and severity index) scoring was used for interpretation of results and it was applied on patients before, during and after sessions. Following 8 weeks of treatment, MASI score reduction was calculated as the primary outcome measure. Standardized photographs were taken using same digital camera at a fixed position and fixed distance from the participant. 2ml of undiluted tranexamic acid (50 mg/ml) was injected intradermally with a 30 gauge insulin syringe into the melasma patches, 1 ml on either side roughly 1 cm apart on each visit which were carried out after every two weeks. A topical numbing agent of 2% lignocaine was applied to the affected area 20 mins. before each session, and to avoid bruising, negative suction was applied on each prick. After the procedure was done, a low potent steroid was applied to minimize procedure associated inflammation. A total number of 4 sessions were carried out with serial assessment of improvement, worsening or no response. Side effects if any were also noted.



1. **MASI score** is calculated by dividing the face into four areas; and each area is weighted such that the forehead (F), right malar area (MR), and left malar area (ML) are 30% each, and the chin (C) is 10%.
2. Amount of pigmentation involved by melasma in these four areas (F, MR, ML, and C) is graded as a numerical value:

- 0 = no involvement
- 1 = less than 10% involvement
- 2 = 10–29% involvement
- 3 = 30–49% involvement
- 4 = 50–69% involvement
- 5 = 70–89% involvement
- 6 = 90–100% involvement

3. Severity of melasma is graded on two factors; darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation on a scale from 0 to 4: The rating scale for both darkness and homogeneity of melasma is:

- 0 = absent
- 1 = slight
- 2 = mild
- 3 = marked
- 4 = maximum

1. MASI score is then obtained by adding the values of sum of severity ratings.
2. **The final formula for MASI Score** = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC.
3. **The total MASI score is 0 to 48**.

Figure 1 MASI score standard guidelines.

Results were finally interpreted after two weeks of the last session. All patients were advised to use cream formulation of sunscreen with SPF 60 regularly.

Sequential changes in the data were analysed using a paired *t*-test. $P < 0.05$ was considered statistically significant. SPSS software (2019 version 26.0, IBM, Armonk, NY, USA) was used.

MASI scoring guidelines MASI scoring used in this study is simple MASI score and it is very differ from modified MASI scoring showed in **Figure 1**.

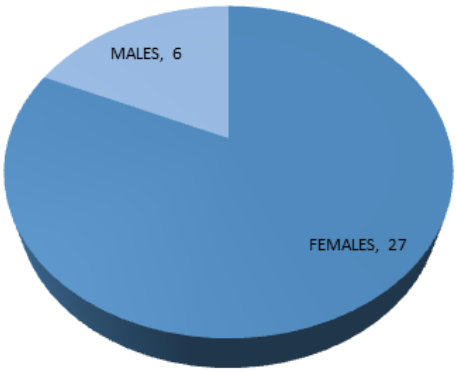


Figure 2

Results

Out of 32 enrolled patients, 6 (18%) were males and 27 (82%) were females **(Figure 2)**.

There were 20 patients 60.60% who had melasma between 1-16 MASI score, 5 patients 15.15% between 16-32 MASI score and no patient of melasma between 32-48 MASI score. MASI score of all patients divided into groups is mentioned in the **Table 1**.

Seven patients initially enrolled discontinued their treatment after 1st and 2nd sessions. The average MASI score of the patients who leave the study was 21.

The maximum results we see in our study is reduction of melasma by 15.7 score and minimum result we see is 0.8 score difference. Average MASI at baseline (0th week) MASI after treatment at 10th weeks **Table 2**.

Improvement in MASI after minus before intradermal tranexamic injection and after treatment is 6.236 **(Table 2)**.

Table 1

MASI score	*No. of patients*	*Percentage*
1-8	8	25%
9-16	13	40.63%
17-24	8	25%
25-32	2	6.25%
33-40	1	3.12%
41-48	0	0%

Table 2

Sr. No	*MASI at 0th Week*	*MASI at 10th Week*	*Difference b/w MASI at 10th week and 0th week*
1	16.2	15.4	0.8
2	4.2	1.2	3.0
3	11.7	4.8	6.9
4	10.4	1.2	9.2
5	15.8	9.6	6.2
6	7.4	2.4	5.0
7	7.8	2.4	5.4
8	12	10.8	1.2
9	11.4	5.7	5.7
10	9.9	4.2	5.7
11	7.2	2.4	4.8
12	14.4	3.6	10.8
13	28.5	12.8	15.7
14	5.6	1.8	3.8
15	5.6	1.8	3.8
16	4.8	1.2	3.6
17	7.8	1.4	6.4
18	12.9	5.2	7.7
19	12.2	5.2	7.0
20	18.3	6.3	12.0
21	13.7	4.2	9.5
22	9.6	1.2	8.4
23	10.2	7.1	3.1
24	13.5	8.4	5.1
25	12	6.9	5.1
Average	11.324	5.088	6.236

Standard Deviation, s: 5.2517888601775

Count, N: 25
Sum, Σx: 271.1
Mean, $\bar{x}$: 11.295833333333
Variance, s^2: 27.581286231884

$$s = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2},$$

$$s^2 = \frac{\Sigma(x_i - \bar{x})^2}{N - 1}$$

$$= \frac{(16.2 - 11.295833333333)^2 + \ldots + (13.5 - 11.295833333333)^2}{25 - 1}$$

$$= \frac{634.36958333333}{24}$$

$$= 27.581286231884$$

SD = √27.581286231884
SD= 5.2517888601775

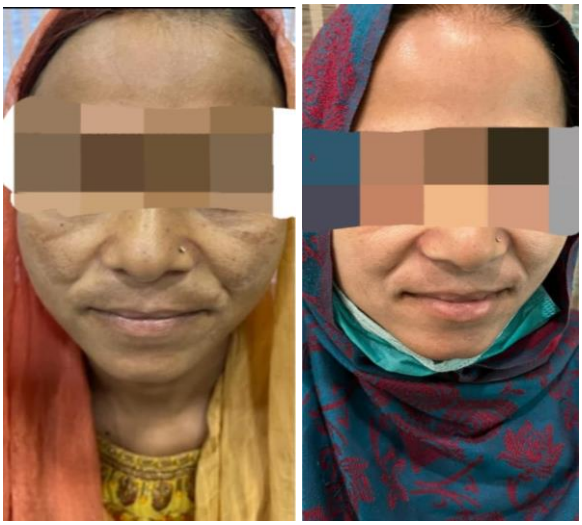


Figure 3

P value is calculated by software SPSS IBM 2019 version 26. The p-value is 0.49989 and the result is significant at P<0.05.

Discussion

Melasma is a common acquired condition of pigmentary disorder causing irregular hyperpigmented patches. It commonly occurs in females with dark skin types living in areas of intense sun light exposure. The treatments for melasma are generally aimed at inhibiting the pathways that synthesize melanin and decrease of melanosome transfer from melanocyte to keratinocytes.[7]

Melasma is often difficult to treat and can be psychosocially detrimental to many patients. Some treatment options including hydroquinone, physical treatments such as chemical peels and low-fluence Q-switched neodymium-doped yttrium aluminum garnet laser (QSNY) need multiple courses over several months are limited by complications including irritant dermatitis, allergic contact dermatitis, post inflammatory hyperpigmentation and nail bleaching.[8]

Tranexamic acid (trans-4-Aminomethyl cyclohexane-carboxylic acid, TA), a plasmin inhibitor, is a synthetic derivative of the amino acid lysine and exerts its effect by competitively inhibiting the activation of plasminogen activator (PA) through reversible interactions with its lysine-binding sites, thus inhibiting PA from converting plasminogen to plasmin. Anti-pigmentary effect of tranexamic acid is achieved by causing shrinkage of dermal vasculature and reduction of melanin synthesis by altering the interaction of keratinocytes and melanocytes and reducing tyrosinase activity. Tranexamic acid inhibits the binding of plasminogen to keratinocytes, consequently reducing the synthesis of prostaglandins, which are well-known stimulators of tyrosinase activity.[9] Owing to this mechanism and structural similarity tranexamic acid was used in our research to see if it actually causes lightening of the melasma.[10]

One study conducted on 88 patients tested the comparative efficacy of oral transamine (250 mg thrice daily oral TA plus HQ 4% cream nightly) with topical hydroxychloroquine alone (HQ 4% cream only) for a period of 3 months of treatment follow up. The overall mean of the MASI score in the intervention group was 1.8 points lower than in the controls (95% confidence interval, 0.36-3.24, *P*=0.015). Side effect occurrence was also similar, but treatment satisfaction was higher in the intervention group than the controls, with 82.2% *vs*. 34.95 of patients reporting moderate-to-complete satisfaction, respectively (*P*<0.001).[11] This study shares similarity to our results in causing improvement in melasma, however in our study no side effects were noted as compared to this study. The difference could be due to the difference in the concentration and the route of administration of the tested drug. The sample size of patients is larger as compared to our study and the follow up time is longer for 3 months whereas our follow up time was only 10 weeks with 2 weeks post treatment assessment.[11,12]

Another study enrolling 23 women 34-60 years of age having melasma, with Fitzpatrick skin type III or IV, used two types of topical TA, i.e. an emulsion containing 2% TA and a nonwoven fabric mask immersed in skin lotion containing 2% TA. Emulsion was applied to the whole face twice a day and the mask three times a week, for 12 weeks. This study also reports improvement in the degree of pigmentation and the extent of erythema in 22 of the 23 patients after 12 weeks of topical TA application, and there was a significant (P<0.05) reduction in m MASI from baseline to any follow-up point. Similarity to the current study is reduction in the melasma but the concentration of tranexamic acid is very less as compared to our study and the formulation is topical emulsion and mask as compared to the intradermal route. Another difference is the application of modified MASI scoring where as we have applied simple MASI.[13]

One comparative study conducted on 55 patients tested efficacy of hydroxychloroquine 4% versus hydroxychloroquine and tranexamic acid on melasma. Daily topical HQ 4% was applied to all patients on one side of face while the other side received additional 1 mL TA (100 mg/ml) intradermal injection with 1 cm intervals by an insulin syringe with a 30-gauge needle at weeks 0, 4, 8, and 12 along with sunscreen cream with sun protection factor of 50. The therapeutic outcomes were significantly better in TA+HQ group than HQ group (p=0.001). This study showed that combination therapy with intradermal tranexamic acid and topical hydroquinone was more effective than conventional therapy (hydroquinone) in the treatment of melasma with less side effects.[11] This study also showed similar results but here tranexamic acid was used as a complimentary therapy to HQ where as in our study, this is used as a sole therapy.

Melasma is a cosmetically disfiguring disease which causes great social and emotional unacceptance. The longer duration of treatments with poor or limited response with many side effects make it a challenge to treat. Despite the advancements, there still remains a desire to formulate newer treatment strategies that could effectively counter this problem. Tranexamic acid used in the concentrated form has yielded very good results with high satisfaction of patients. Therefore, this is a very good alternative to choose but the prevention of relapse still remains an ultimatum.

Conclusion

Intradermal tranexamic acid in concentrated form 100mg/session causes major and statistically significant improvement in MASI scores as achieved in our study with no or minimal side effects. Therefore, this should be considered as an effective treatment option either as first line or in the patients recalcitrant to treatment.

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