

Treatment of Melasma Cases by Oral Tranexamic Acid: A Randomized Control Trial

Karim ATMR¹, Sadeque SP², Ferdous A³, Khan MAL⁴, Rahman MH⁵, Rafi A⁶, Masum A⁷

DOI: <https://doi.org/10.3329/jafmc.v14i2.45896>

Abstract

Introduction: Melasma is a great challenge for a dermatologist as its treatment is unsatisfactory and recurrence is high. Treatment of melasma using oral tranexamic acid is a novel concept.

Objectives: To compare the efficacy of oral tranexamic acid with routine topical therapies for the treatment of melasma.

Materials and Methods: This prospective, interventional, randomized controlled trial was conducted among 130 melasma patients in the Department of Dermatology, Combined Military Hospital, Cumilla from June 2016 to June 2017. The patients were divided into two groups consisting of 65 patients each. The first group (Group A) was given routine treatment measures and oral Tranexamic Acid while the second group (Group B) was treated only with routine topical measures. Capsule Tranexamic Acid was prescribed at a dose of 250 mg twice a day for three months and cases were followed during the course of treatment. The response was evaluated on the basis of Melasma Assessment Severity Index (MASI).

Results: A statistically significant decrease in the mean Melasma Assessment Severity Index from baseline to 8th and 12th weeks was observed among group A patients (11.08±2.91 vs 8.95±2.08 at week 8 and vs. 7.84±2.44 at week 12; (p<0.05 for both). While among group B patients the decrease in mean score was significant at 8 weeks and insignificant at 12 weeks follow up (11.60±3.40 vs 9.9±2.61 at 8 weeks and vs. 9.26±3 at 12 weeks; p<0.05 for former but p>0.05 for later).

Conclusion: Oral Tranexamic acid provides rapid and sustained improvement in the treatment of melasma.

Key-words: Melasma, Tranexamic acid.

Introduction

Melasma is characterized by irregular light to grey-brown macules and patches on sun exposed skin¹ commonly affecting the cheeks, forehead, upper lip, nose, chin and occasionally forearms. It is a common acquired disorder of pigmentation and is known to occur in all skin types, all

ethnic groups and both sexes. It is relatively more common in darker skin type (III and IV) and more in women of childbearing age. The exact aetiology of melasma is unknown, but exposure to UV irradiation and genetic factors are considered as main causes in addition to endocrine factors (pregnancy, hormonal therapy and ovarian dysfunction), drugs (phenytoin, phototoxic drugs), cosmetics, vascular and systemic diseases like thyroid dysfunction and anaemia of multifactorial origin. These factors lead to an increased synthesis of melanosomes in melanocytes and their transfer to keratinocytes. Melasma lesions typically fade in winter and aggravate in summer. Chloasma (melasma related to pregnancy) usually diminishes within a few months of delivery but melasma lesions due to oral contraceptives are usually persistent². Three clinical patterns of melasma are recognized: malar (most common), centrofacial and mandibular³. Classification of melasma is based on visible light, Wood's light and lesional histology which is as follows: epidermal, which has increased melanin predominantly in basal and suprabasal layers of the epidermis with pigment accentuation on Wood's lamp. The dermal type has perivascular melanin laden macrophages in the superficial and deep dermis and does not accentuate with Wood's lamp. The mixed variety has elements of both and appears as a deep brown colour with Wood's lamp accentuation of only the epidermal component³. However, it is believed that usually, melasma has both components.

Treatment of melasma can be very frustrating and challenging because the aim is to obtain a decrease in melasma pigment without hypopigmentation. Till date, none of its existing treatment modalities has provided quick and sustained result. Today topical hydroquinone is considered to be the gold standard among topical treatments of melasma⁴. Prevention of UV radiation, topical bleaching agents, chemical peel and light-based therapies are the currently existing plethora of remedies. Addition of tranexamic acid (TXA) for the treatment of melasma is a novel concept. Previously used as an anti-fibrinolytic agent, TXA is

1. Lt Col A T M Rezaul Karim, MBBS, DDV, MCPS, FCPS, Associate Professor of Dermatology, AFMC, Dhaka (E-mail: drreza1031@yahoo.com) 2. Dr Shayesta Parvin Sadeque, MBBS, DGO, Assistant Professor of Gynae&Obs, Army Medical College, Cumilla 3. Dr Afreen Ferdous, MBBS, MPhil, Assistant Professor of Physiology, East-West Medical College, Uttara, Dhaka 4. Brig Gen Md Abdul Latif Khan, MBBS, DDV, FCPS, Adviser Specialist in Dermatology, CMH, Dhaka 5. Brig Md Habibur Rahman, MBBS, FCPS, Professor of Medicine, AFMC, Dhaka 6. Col Ahmed Rafi, MBBS, MPH, MPhil, Commandant, CMH, Cumilla 7. Lt Col Abdullah Masum, MBBS, DA, FCPS, Classified Specialist in Anaesthesiology, CMH, Cumilla.

recently found to inhibit plasminogen-keratinocyte interaction decreasing tyrosinase activity leading to decreased melanin synthesis from the melanocytes^{5,6}. Very few clinical trials have been conducted regarding the efficacy of oral TXA for the treatment of melasma. This study is thus conducted to compare the efficacy of oral TXA along with routine treatment measures for the treatment of melasma.

Material and Methods

It is a prospective, interventional, randomized controlled trial conducted among 130 (87 females and 43 males) melasma patients in the Department of Dermatology, Combined Military Hospital, Cumilla from June 2016 to June 2017. This study was conducted after taking authorization from the institutional review committee. Patients age ranged from 17-55 years and were checked for bleeding time, clotting time, platelet count before they were included in the study. Patients with abnormal parameters and patients who discontinued the treatment or wanted chemical peel or laser for better response were excluded from the study. The type of melasma was graded with Wood's lamp and dermatoscopic examination. Patients were randomly divided into two groups consisting of 65 patients each using a random number table. The first group (Group A) was added on with oral TXA along with routine topical treatment measures while the second group (Group B) was treated only with routine topical measures. Topical treatment included topical hydroquinone and sunscreen according to the skin types. Capsule TXA ((Trans-4-aminomethyl cyclohexanecarboxylic acid)) was prescribed at a dose of 250 mg twice a day for three months and cases were followed up every four weeks till the end of the third month. The response was evaluated on the basis of Melasma Assessment Severity Index (MASI) score⁷. MASI score was calculated during the start of therapy (baseline) and at the end of 8th and 12th weeks.

MASI is a scoring system introduced by Kimbrough-Green CK et al used to quantify the severity of melasma⁷. Four areas of the face are evaluated: forehead (F), right malar region (MR), left malar region (ML) and chin (C), corresponding to 30%, 30%, 30%, and 10% of the total face respectively. Amount of pigmentation involved by melasma in these four areas (AF, AMR, AML, and AC) is graded as a numerical value: 0: no involvement; 1: less than 10% involvement; 2: 10–29%; 3: 30–49%; 4: 50–69%; 5: 70–89% and 6: 90–100%. The severity of melasma is graded upon two factors; darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation. These are assessed on a scale from 0 to 4. The rating scale for both darkness and homogeneity of melasma is as follows; 0: absent; 1: slight; 2: mild; 3: marked; and 4: maximum. MASI score is then calculated according to the following formula: $MASI = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML$

+ HML) AML + 0.1 (DC + HC) AC. The maximum score for MASI can be 48 while the minimum can be 0. SPSS 16 was used for the statistical analysis. Mean MASI scores were compared with students' T-test and statistical significance was compared. Patient satisfaction score was subjectively graded on the basis of a four-point Likert scale: excellent, good, fair, and poor. Possible side effects of TXA were noted on follow up of patients.

Results

Among the study participants (n=130), both groups Group A (n=65) and Group B (n=65) had the majority of female participants 44 (67.69%) and 43 (66.15%) respectively. In Group A patients, epidermal melasma was seen in 47 (72.31%) followed by mixed type 11 (16.92%) and dermal 07 (10.77%). In Group B patients, the majority had epidermal melasma 40 (61.54%) followed by mixed type 18 (27.69%) and dermal 07 (10.77%). Distribution of melasma in Group A was frontal 07 (10.77%), centrofacial 51 (78.46%), chin 07 (10.77%) and in Group B, frontal 07 (10.77%), centrofacial 54 (83.07%), chin 04 (6.15%) respectively (Table-I). In Group A patients, 36.90% of participants showed Good and 45.40% showed Excellent improvement and the satisfaction score was 11.08±2.91 at baseline vs 8.95±2.08 at week 8 and 7.84±2.44 at week 12 (Figure-1). Group B patients, 40% of participants showed Satisfactorily and 32.30% showed Good improvement and the satisfaction score was 11.60±3.40 at baseline vs 9.9±2.61 at 8 weeks and vs. 9.26±3 at 12 weeks (Figure-2). The improvement in Group A patients at 8th and 12th week was statistically significant p-value <0.05% but in Group B patients, findings at 8th week only were statistically significant.

Table-I: Gender of patients, pathological type and distribution of melasma (N=130)

Clinical Profile		Group A		Group B	
		n=65	%	n=65	%
Gender	Male	21	32.30	22	33.85
	Female	44	67.69	43	66.15
Type of Melasma	Epidermal	47	72.31	40	61.54
	Dermal	07	10.77	07	10.77
	Mixed	11	16.92	18	27.69
Distribution	Frontal	07	10.77	07	10.77
	Centrofacial	51	78.46	54	83.07
	Chin	07	10.77	04	6.15

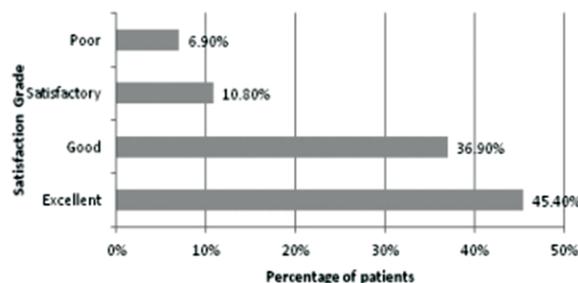


Figure-1: Satisfaction scores for Group A patients at 12 weeks

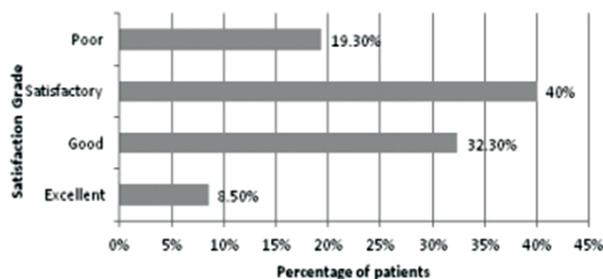


Figure-2: Satisfaction score for Group B patients 12 weeks

Discussion

Clinical trials have shown that topical medications demonstrate some efficacy in the epidermal type but not in the dermal or mixed type of melasma^{8,9}. Prolonged application, slow response, limited effects and undesirable recurrence are the major disadvantages of topical therapies causing patients to abandon the treatment. Also, topical bleaching agents may irritate the skin and develop post-inflammatory hyperpigmentation or result in exogenous ochronosis. Laser-assisted treatment is a good method however recurrence remains disappointing¹⁰. The most effective and safe treatment for melasma is thus yet to be explored. TXA is used as a haemostatic agent due to its anti-fibrinolytic action¹¹. It is a synthetic derivative of the amino acid lysine used to treat and prevent excessive bleeding. Nijor T¹² first studied and reported the action of TXA on melasma in 1979. However, limited studies are found in the literature regarding the use of TXA on melasma. Maeda K et al studied the role of TXA in human melanocyte and keratinocyte cultures^{11,12}. Their results revealed that TXA inhibits melanin synthesis in epidermal melanocytes' tyrosinase activity by blocking the interaction of melanocytes and keratinocytes by inhibition of plasminogen/plasmin system. TXA acts by attaching to the lysine-binding sites of plasmin and plasminogen and also prevents ultraviolet rays induced pigmentation.

Similar study as this one was conducted on a split-face based trial with topical TXA gel¹³. Their result showed lightening of pigmentation but was insignificant in comparison to the control group. Also, topical TXA produced erythema. Lee JH et al injected localized intradermal microinjection of TXA for melasma and found statistically significant lightening⁹. Histological evaluation following oral and topical TXA for melasma was done which concluded that TXA decreases epidermal pigmentation associated with melasma and also reverses melasma-related dermal changes, such as vessel number and increased numbers of mast cells¹⁴. Uses of oral TXA for melasma in similar dose have been tried in Chinese population and authors recommend TXA to be an effective and safe therapy for the treatment of melasma¹⁵. The dose of oral TXA used in melasma is far less than that prescribed for its haemostatic action. Venous thromboembolism, myocardial infarction, cerebrovascular accidents and pulmonary embolism are some reported complications in a haemostatic dose of

TXA. It is contraindicated for patients having acquired defective colour vision, an active intravascular clotting condition, and hypersensitivity to TXA. Hence, proper patient selection ruling out any risk factor resulting in hypercoagulability is of pivotal importance prior to the start of therapy.

The results of this study are consistent with the results of related studies where successful lightening was observed following oral TXA administration. Despite the lack of objective measurement in the improvement, a good clinical outcome of melasma was observed. Longer duration follow-up and randomized controlled trials involving a larger number of patients are recommended for further exploration of the efficacy of TXA in the near future. Oral TXA being a non-invasive, non-irritating drug with low side effect profile, can be routinely recommended in low dose to the patients with melasma.

Conclusion

Addition of oral TXA to the routine treatment measures provides a rapid and better lightening in patients with melasma. Low dose oral TXA is thus recommended for the treatment of melasma.

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