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EFFICACY OF 10% TOPICAL TRANEXAMIC ACID IN MELASMA - A RANDOMIZED PLACEBO-CONTROLLED SPLIT FACE STUDY

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ABSTRACT: Introduction: Melasma is a common facial pigmentary dermatosis in Indians. In spite of various treatment modalities, treatment of melasma is often challenging and recalcitrant. In this context, the present study was carried out to elucidate efficacy and safety of topical 10% Tranexamic acid (TXA) in melasma treatment. **Materials and Methods:** 40 Melasma patients with malar type were enrolled in the 12 weeks study. They were advised to apply 10% Tranexamic acid cream and placebo to the right and left cheek respectively along with sunscreen. MASI score, a subjective measurement was determined as a clinical outcome of study before and after treatment. **Results:** After treatment, there was a statistically significant reduction of baseline mean MASI score (Melasma Area and Severity Index score) of the right side of cheek (Tranexamic acid) 5.12 ± 1.78 to 4.01 ± 1.51 (P=0.000). Patient and physician satisfaction score revealed good response in the majority of the study population. **Conclusion:** Topical 10% Tranexamic acid is effective and safe for melasma treatment.

INTRODUCTION: Melasma is a common acquired pigmentary disorder of the skin, manifests as tan brown macules and patches symmetrically involving the sun-exposed areas of the face and neck. It occurs in both sexes but more commonly observed in women with fitzpatrick skin type IV-VI mainly Asians [1]. The etiopathogenesis of melasma is multifactorial. Genetic susceptibility, ultraviolet (UV) light exposure, pregnancy, sex hormones, contraceptive pills, thyroid disease, cosmetics, phototoxic drugs are involved in the pathogenesis of melasma [2]. In the hierarchy of melasma therapies, results are controversial because of its multifactorial etiology.

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Recently some researchers found Tranexamic acid [TXA] a traditional antifibrinolytic agent, as a novel component in melasma treatment. TXA claimed to have hypopigmentary effect when administered either orally, topically or intra-dermally [3]. There are very few controlled trials in the literature regarding the role of TXA in melasma. So the current study was conducted to evaluate the efficacy and safety profile of TXA in melasma treatment in the Indian scenario.

MATERIALS AND METHODS: A prospective, randomized, interventional, placebo-controlled split-face study was conducted in the outpatient dermatology department of GSL Medical College and General Hospital, Rajahmundry. After Institute ethics committee approval GSLMC/ RC:80/EC/01/16, 40 patients aged 18-50 years with bilaterally symmetrical malar distribution melasma were included in the study. After obtaining informed consent from the study subjects, patients were classified into epidermal, dermal and mixed

by wood's lamp examination. Patients on hormonal therapy or oral contraceptives pills, history of coexisting endocrinopathies, pregnant or lactating mother, known allergic to Tranexamic acid, allergic to sunscreen, a previous topical treatment for melasma within 4 weeks, on any oral Tranexamic acid within 3 months were excluded from the study. All the study participants were allocated to apply A cream (10% TXA) on the right cheek and B cream (placebo) on the left cheek (only over the lesions). Both creams (TXA and Placebo) were packed in identical containers. The patients were instructed to apply both creams, twice daily on each side of the face for 12 weeks. In the morning hours, they were instructed to apply sunscreen 30 min after applying the study medications.

MASI score, a subjective measurement was determined as a clinical outcome of study before and after treatment. According to the MASI score, the whole face is divided into four areas: 30% the forehead, 30% RM, 30% LM, and 10% chin (C). The grade of melasma severity was determined by three variables: A = percentages of total area involved on a scale of 0 (no involvement) to 6 (90-100% involvement), D = darkness on a scale of 0 (absent) to 4 (maximum), and H = homogeneity of hyperpigmentation on a scale of 0 (minimal) to 4 (maximum). The MASI score is then calculated by the following equation: = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC. MASI score was calculated only for malar areas. Photographs were taken at the baseline and the end of 12 weeks so that the clinical investigator can assess melasma improvement and grade with a global physician score. The patient's self-assessment was graded along four scales: 1 = >75% lightening (excellent), 2 = 51-75% (good), 3 = 26-50% (fair), and 4 = 0-25% (poor). Statistical software SPSS v.16.0 was used for statistical analysis. Results were presented as the mean ± standard deviation for quantitative variables and summarized by absolute frequencies and percentages for categorical variables. The paired t-test was applied to assess changes in the MASI score at baseline and the end of 12 weeks. $P<0.05$ was considered statistically significant.

RESULTS: Out of 40, 38 patients completed the study. In the study population, 87% were female, and 13% were males. The majority (61%) were in the age group of 31- 40 yrs. The mean age of the study subjects was 40.16 ± 5.76 years, and the mean duration of melasma was 3.3 ± 2.87 yrs. On wood's lamp examination majority was found in epidermal type **Table 1**.

TABLE 1: BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

Variables [n=38]	No of patients (%)
Gender	
Female	33(87%)
Male	5(13%)
Age (yrs)	
21-30	4(11%)
31-40	23(61%)
>40	11(28%)
Duration of melasma (yrs)	
<1	5(13%)
1-5	26(68%)
>5	7(19%)
Mean ±SD	3.3±2.87
Type of melasma	
Epidermal	24(63%)
Dermal	5(13%)
Mixed	9(24%)
Family history of melasma	5(13%)

Table 2 represents that there was a significant statistical reduction of MASI score on right side of cheek (TXA) at the end of 12 weeks when compared to baseline (P=0.000). On the left side of the cheek (placebo) the mean MASI score reduced from 5.28 ± 1.57 to 5.09 ± 1.72, which is found to be statistically insignificant (P=0.06).

TABLE 2: MEAN MASI SCORE AT BASELINE VERSUS TREATMENT ENDPOINT

Area of melasma	Before treatment (Mean ± SD)	After treatment (Mean ± SD)	'P' value
Right side of cheek (TXA)	5.12 ± 1.78	4.01 ± 1.51	P=0.000*
Left side of cheek (placebo)	5.28 ±1.57	5.09 ± 1.72	P=0.06

*P<0.05 is considered statistically significant.

Physician global assessment score analysis revealed that the majority of patients showed good response **Table 3**. Patients when assessed regarding their satisfaction, the majority (58%) opined good improvement **Table 4**. In the study, it was also observed that there is no correlation between the efficacy of TXA and patient's age, and duration of melasma. The side effects of treatment were

minimal such as mild erythema in 3 study subjects and burning in 2 subjects. These side effects were tolerable and transient, and the patients did not demand discontinuation of treatment.

TABLE 3: PHYSICIAN ASSESSMENT SCORE AFTER 12 WEEKS OF TREATMENT

Physician Grade			
Excellent	**Good**	**Fair**	**Poor**
2(5%)	21(55%)	11(29%)	4(11%)

TABLE 4: PATIENTS SATISFACTION SCORE

Satisfaction Grade			
Excellent	**Good**	**Fair**	**No response**
3 (8%)	19(50%)	11(29%)	5(13%)

DISCUSSION: Treatment of melasma is challenging because it is often recalcitrant to therapy. TXA is now a novel therapeutic modality in the treatment of melasma. Nijor in 1979 first reported TXA to inhibit UV plasminogen keratinocyte interaction leading to decrease in melanocyte tyrosinase activity and further diminished melanin synthesis. TXA (trans-4-aminomethyl cyclohexane carboxylic acid) acts by attaching to the lysine-binding sites of plasmin and plasminogen and prevents ultraviolet rays induced pigmentation [4]. TXA prevents the conversion of matrix-bound vascular endothelial growth factor (VEGF) into freely diffusible forms which lead to angiogenesis [5].

Thus, TXA is claimed to have anti-inflammatory and whitening effects when administered either systemically or topically [4]. When administered orally, side effect like oligomenorrhoea, palpitation, gastrointestinal upset was reported. So, topical TXA is a much safer option. Several studies have confirmed the effectiveness of TXA in melasma by various modes of administration [6, 7]. In this aspect, it was observed that there are studies with 5%, 3% and 2% topical TXA in melasma but no studies in the literature with a topical 10% TXA. In the previous studies, the results are variable. Hence, the study has been taken up to observe the efficacy and tolerability of topical 10% TXA in melasma.

In a study by Ebrahim *et al*., in Iranian patients, they compared topical 3% TXA and 3% hydroquinone + 0.05% dexamethasone for 12 weeks, and a significant decreasing trend was reported in MASI score of both groups. The physician assessment showed good response in 68% patients which were comparable to the current study. So, they reported that the efficacy of TXA is similar to hydroquinone [8]. In another Indian study, they compared both topical and oral TXA and recommended TXA to be an effective and safe therapy for the treatment of melasma [9]. In another split-face study, who compared the therapeutic effect of 5% liposomal TXA with 4% hydroquinone in 30 women and found more pigment reduction in TXA applied side [10].

Steiner *et al*., in a comparative study found that topical TXA was more effective than intralesional TXA [11]. Kim *et al*. studied the effects of 2% topical TXA by immunohistochemical study and found effective. However, in contrast to our study the decrease in pigmentation was minimal and not statistically significant, but the improvement was apparent by 4 weeks. The difference could be due to the lower strength of topical TXA used and lack of a placebo group. Their study suggested that prolonged treatment time is required for effect [12, 13], hence in the present study, we increased the strength of TXA and found effective with a very minimal side effect. TXA was claimed to have anti-angiogenic and anti-inflammatory effects when administered either systemically or topically [14]. Few studies were also carried to evaluate the efficacy of oral Tranexamic acid.

Most of the studies showed significant improvement in MASI score, but systemic side effects like oligomenorrhoea, palpitation, gastrointestinal upset were reported. So, topical Tranexamic acid is a much safer option. Our results correspond with the above-related studies where successful lightening was observed. It was also found to be more effective in epidermal type than in dermal melasma. A few side effects like mild erythema and burning were noticed which were transient and insignificant. Small sample size and lack of objective measurement as an evaluating tool were limitations of the study. However, for a more convincing clinical trial a split face design, regular use of sunscreen, subjective and validated clinical outcome measures like in current Indian study determine a better exposure to treatment. Further studies with larger sample size, multicentric study and follow up are required to study Tranexamic acid treatment outcome in melasma.

CONCLUSION: Topical 10% Tranexamic acid as monotherapy is effective and safe in the management of melasma. The study recommends its use in Indian melasma patients.

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