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COMPARATIVE STUDY OF EFFICACY AND SAFETY OF ORAL TRANEXAMIC ACID WITH TOPICAL TRIPLE COMBINATION VERSUS TRIPLE COMBINATION ALONE IN MELASMA

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ABSTRACT: Objective: Melasma is a chronic acquired hyper melanosis of skin, involving sun exposure areas of the face and neck. Even with various treatment modalities, melasma recurs and long-term treatment is associated with many side effects. Tranexamic acid, the antifibrinolytic agent is a drug of research for melasma, as it inhibits melanogenesis. Hence, the present study compares the efficacy and safety of oral Tranexamic acid (TXA) with topical Triple Combination Cream (TCC) containing fluticasone propionate 0.05%, tretinoin 0.025% and hydroquinone 2% versus topical triple combination alone in the treatment of melasma. **Methods:** About 120patients who met the inclusion criteria were randomly assigned into two groups of 60 patients each. Group A was treated with TCC at night and group B received oral TXA 500mg once daily morning and TCC at night for 8weeks. All patients were advised to apply sunscreen with SPF 50. The follow-up was done in the 4th and 8th week and MASI score (efficacy) and side effects if any, like deranged clotting time, bleeding time and ophthalmology examination (safety) were done. SPSS software was used for statistical analysis and categorical data was analyzed using the chi-square test and the Fischer-exact test. P-value <0.05 was considered significant. **Results:** Though TCC showed a good response in the 8th week, the TCC+TXA group had a faster, better and more sustained rate of response in 4th and 8th weeks with highly significant results with p-values of <0.001 and <0.0001 respectively. **Conclusion:** TXA is an effective add-on in the treatment of melasma.

INTRODUCTION: Melasma is a neglected skin condition, which is described as acquired localized chronic hyper melanosis, which affects parts of the face and neck that are exposed to the sun. It is distinguished by patches and macules vary in hue from light to deep brown.

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Darker-skinned people with Fitzpatrick IV to VI skin types are more likely to have it [1, 2]. Disfiguration due to melasma also affects the social well-being of a person, creating poor life quality and decreases one's self-confidence. Therefore, it must be treated [3].

The prevalence of melasma in India varies from 1.5% to 33.3%, with pregnant women accounting for 50-70% of cases [4]. Among available treatments, triple combination creams (TCC) are the primary conventional option for managing melasma since, the introduction of this combination therapy by

Kligman and Willis, which contains tretinoin (0.1%), hydroquinone (5%), and dexamethasone (0.1%), many doctors worldwide utilized it, modifying steroid with changing the concentration of the additional two components to lessen adverse effects [5]. Among various steroid combinations, Fluticasone serves as a mild steroid combination but with good efficacy similar to the potent steroids. Previous research demonstrated that Fluticasone (0.05%) used once daily was just equally efficient as betamethasone (0.12%) applied two times daily, with a decreased incidence of skin atrophy and no systemic side effects after prolonged use [6]. Another research, Mometasone, a strong steroid, demonstrated comparable efficacy to Fluocinolone in a study comparing the two, with no significant adverse effects such as skin atrophy or cortisol suppression [7].

A perfect cure for melasma remains elusive, as no single medication or combination has demonstrated consistent efficacy. Also, most of the treatment takes four to six weeks to start showing some effect and long treatment duration can cause side effects. Even after such a lengthy course of treatment, the condition is often resistant to current medications, and if not well maintained, there is a risk of recurrence [8]. A perfect and efficient medication therapy is always required in light of the disadvantages.

An antifibrinolytic class of drug, tranexamic acid (TXA) is a synthetic derivative which stops excessive bleeding by blocking the lysine binding site of plasminogen molecule [9]. Plasminogen also increases the melanocyte activity and is also found in keratinocytes of the epidermis and dermis. Plasminogen facilitates the release of precursors of phospholipase A2 and growth promoting factors, both of which are necessary for the synthesis of melanin. Therefore, TXA prevents melanogenesis by decreasing the amount of time that keratinocytes and melanocytes come into contact by inhibiting the keratinocyte plasminogen molecule [10]. According to some reports, TXA can lessen pigmentation that are refractory too [11]. Few studies have evaluated the combination of TXA and fluticasone-based TCC in the Indian population. Therefore, the present work was undertaken to compare the efficacy and safety of triple combination cream containing fluticasone propionate (0.05%), tretinoin (0.025%) and hydroquinone (2%) along with oral tranexamic acid opposed to triple combination cream alone to treat melasma.

METHODS: A comparative, prospective, open-label study was conducted in the Dermatology OPD of a tertiary care hospital over a period of 18 months after the approval from IEC. (IEC Reg. No.IECJJMMC/IEC/). Before participation, detailed written and informed consent was taken from every participant involved in the study.

Study subjects of either gender between 18-50 years of age who are newly diagnosed or a refractory case of melasma and willing for consent were included in the study. Women on hormone replacement therapy, oral contraceptives, or those who were pregnant, nursing, or planning to conceive were excluded. Additionally, individuals with bleeding disorders, anticoagulant therapy, cerebrovascular disease, major liver or cardiovascular diseases, a history of colour vision defects, a history of drug allergies, or a history of other depigmenting treatments were excluded.

Calculation of the sample size was planned according to this formula, $(Z\alpha)^2 p(p-1)/d^2$ in which, Zα (Z variate of α error) =1.96 (for 0.05 α), d (error difference) = 10%, p is the prevalence (17.4%) [12]. A projected rate of dropout of 10% was considered based on the pilot study conducted where we experienced challenges for follow-up of patients and around 120 participants who fulfilled the inclusion criteria were enrolled. A thorough medical and personal history was obtained using a pre-made case record form. A Wood's lamp test was conducted to identify lesion types and melasma, and photographs were taken prior to initiating treatment. Later the participants were randomly divided into two separate groups each containing 60 patients using computer generated numbers. For a duration of eight weeks, patients in group A received treatment with triple combination cream (TCC) that contained fluticasone propionate 0.5mg (0.05%), tretinoin 0.25mg (0.025%), and hydroquinone 20mg (2%). Meanwhile, patients in group B received tranexamic acid (500 mg) orally daily morning in addition to triple combination cream (TXA + TCC) that contained fluticasone propionate 0.5mg (0.05%), hydroquinone 20mg

(2%) and tretinoin 0.25mg (0.025%) topically at night. The study participants of both the groups were instructed to apply Sunscreen with SPF50. The MASI score was determined from all the participants in the beginning, four, and eight weeks, and the follow-up was scheduled for the fourth and eighth weeks **Fig. 1.**

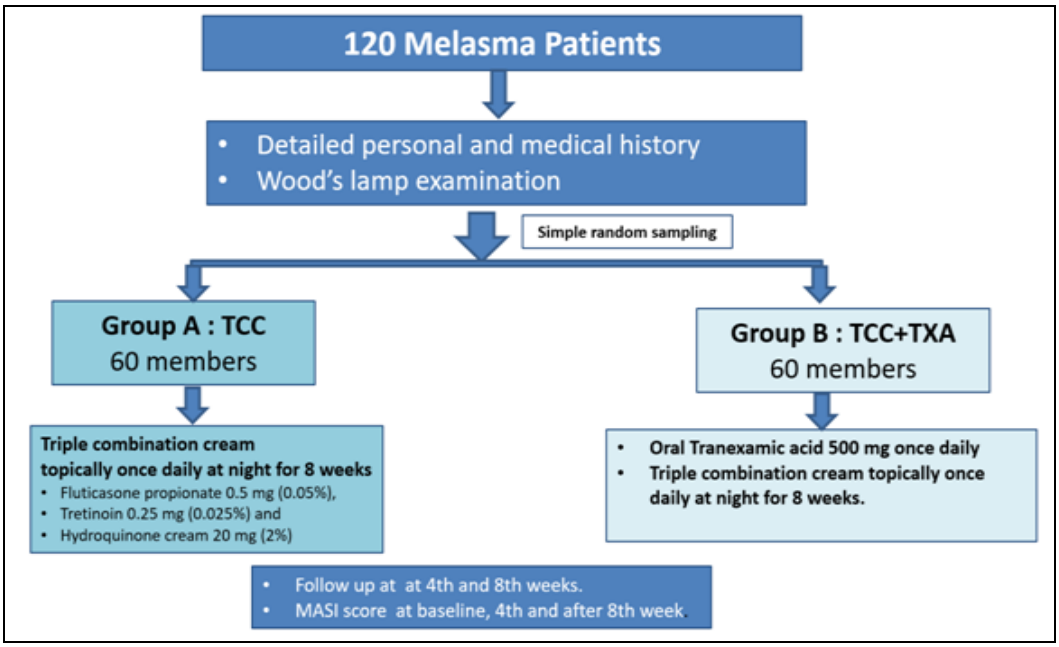

FIG. 1: RANDOMIZATION AND GROUPING OF PARTICIPANTS

Group A: Triple combination cream (TCC); Group B: Triple combination cream + Tranexamic acid (TCC + TXA). The Melasma Area and Severity Index (MASI), which was first developed by Kimbrough Green *et al.*, was used to compare the effectiveness of the treatments [13]. As a result, the face was separated into four areas: 30% for the forehead (F), 30% for the right (RM) and left malar (LM) regions, and 10% for the chin(C). Subsequently, every area was assigned a numerical value (A 0-6) and the sum of melasma darkness (D 0-4) and homogeneity (H 0-4) in percentage was then multiplied with a numerical value for each part of the face **Table 1.**

TABLE 1: MASI SCORE

Score	Darkness (D)	Homogencity (H)	Area (A)
0	Absent	Minimal	No involvement
1	Slight	Slight	<10%
2	Mild	Mild	10-29%
3	Marked	Marked	30-49%
4	Maximum	Maximum	50-69%
5	Not applicable	Not applicable	70-89%
6	Not applicable	Not applicable	90-100%

The three factors of percentage of Total Area Involved (A), Darkness (D), and Homogeneity (H) were then used to examine the degree of melasma in each of these four areas (forehead, right malar, left malar, and chin). The MASI score was then calculated by adding the values acquired. MASI Score = 0.3(DF+HF) AF + 0.3(DMR+HMR) AMR + 0.3 (DML+HML) AML + 0.1(DC+HC) AC. Based on the percentage decrease in MASI score, each patient's response was assessed during the follow-up as follows: No response: no change in MASI score; mild response: a score drop of less than 25%; Moderate response: score decline of >26–<50%; Good response: score decline of >51-<75% and Very good response: greater than >76% drop in MASI score. Patients were asked about typical, well identified side effects, like erythema, irritation or atrophy of skin, or any unidentified negative symptoms, in order to assess safety. Coagulation tests, including bleeding and clotting times were conducted at each follow-up, along with fundoscopic examinations to evaluate the safety of

TXA. Any deviation from normal values was observed.

Statistical Analysis: With the help of MS Excel, the data was entered and SPSS software v16.0 was used for analysis. Frequency and percentage were used to express categorical data. Student t-test, chi-square test and Fischer exact test was used to express the association of variables. For continuous variables, the mean and standard deviation were calculated. Considered 95% confidence interval in the analysis.

RESULTS: Out of 120 participants with 60 in each group, the major study population 34 (56.7%) was between the ages of 31-40 years in both the groups, with 13(27.1%) of group A and 17(28.3%) of group B instances being between the ages of 41-50years and 13(21.7%) of group A and 09 (15%) of group B being between the ages of 20-30 years. Melasma was predominantly observed in females, with 115 (95.8%) participants being women across both groups. Melasma was correlated with marital status with statistically significant p value <0.001, as 116 participants (96.66%) were married and only 4 participants (3.33%) were unmarried.

The duration of melasma was below 5years among 70cases (58.33%) and between 6 -10years in 44 cases (36.66%) and between 11-20 years in 6 (5%) cases presenting it as a chronic condition. About 48 (40%) of the study participants had history of melasma onset while they were pregnant while, rest 72(60%) should no correlation with pregnancy (p=0.264).

In about 97(80.83%) cases, sun exposure was positively correlated with melasma. Exposure to sunlight exacerbated pre-existing lesions and increased the prevalence of melasma. About the type, Dermal type of melasma was the common one in about 66 cases (55%) followed by Epidermal type in 33 cases (27.5%) and Mixed type in 21 cases (17.5%). Malar (ML) pattern was commonly seen in 62cases (51.66%), followed by the Centro facial (CF) pattern with 58 cases (48.33%) **Table 2.**

TABLE 2: SOCIO-DEMOGRAPHIC PARAMETERS

Socio-Demographic parameters		Group A 60(%)	Group B 60(%)
Age in years	20-30	13 (21.7%)	09 (15.0%)
	31-40	34 (56.7%)	34 (56.7%)
	41-50	13 (27.1%)	17 (28.3%)
Gender	Male	2 (3.3%)	3 (5.0%)
	Female	58 (96.7%)	57 (95.0%)
Marital status*	Married	58 (96.7%)	58 (96.7%)
	Unmarried	2 (3.3%)	2 (3.3%)
Sun exposure	Present	46 (76.7%)	51 (85.0%)
	Absent	14 (23.3%)	09 (15.0%)
Wood's Lamp	Dermal	30 (50.0%)	36 (60.0%)
	Epidermal	20 (33.3%)	13 (21.7%)
	Mixed	10 (16.7%)	11 (18.3%)

*Marital status showed a positive correlation with significant p value 0.001.

The mean MASI score decreased from 17.8 to 7.60 in Group B by 8 weeks, compared to a reduction from 18.62 to 10.97 in Group A. In contrast with group A, group B had greater improvement, as stated in **Table 3.**

TABLE 3: MEAN MASI SCORE

Group	Group A	Group B	P value*
Baseline	18.62±9.13	17.82±8.78	-
4th week	14.03±6.86	10.77±5.62	0.04
8th week	10.97±5.46	7.60±4.69	0.001

Group A: Triple combination cream; Group B: Triple combination cream + Tranexamic acid *Student t test

From the beginning to the fourth week, Group B percentage change was 38.92% and Group A was 24.4%. During the eighth week, compared to group A 40.77% change from baseline, group B was 58.05%. As stated above, group B has improved more than group A in both the fourth and eighth weeks as mentioned in **Fig. 2.**

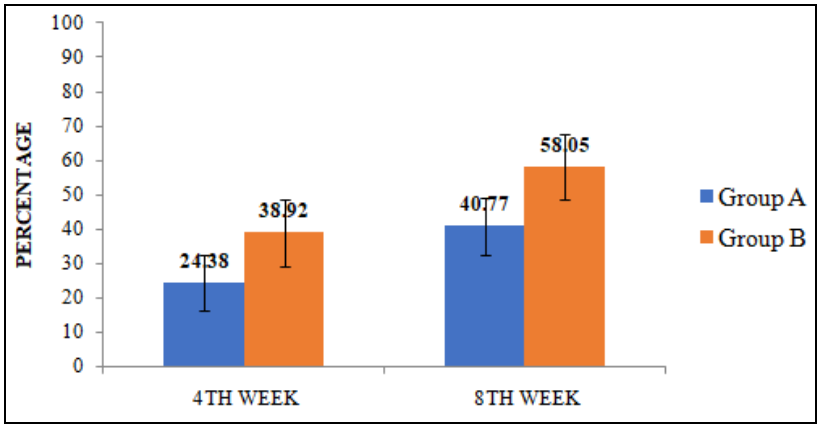

FIG. 2: PERCENTAGE CHANGE OF MASI SCORE FROM BASELINE. Group A: Triple combination cream; Group B: Triple combination cream + Tranexamic acid

At the fourth-week follow-up, 41(68.3%) of participants in Group A showed a mild response, while 19 (31.7%) demonstrated a moderate response. Similarly, among group B, as shown in **Fig. 3**, 6(10%) of the cases had a mild response, 50 (83.3%) had a moderate response and 4 (06.7%) had a good response.

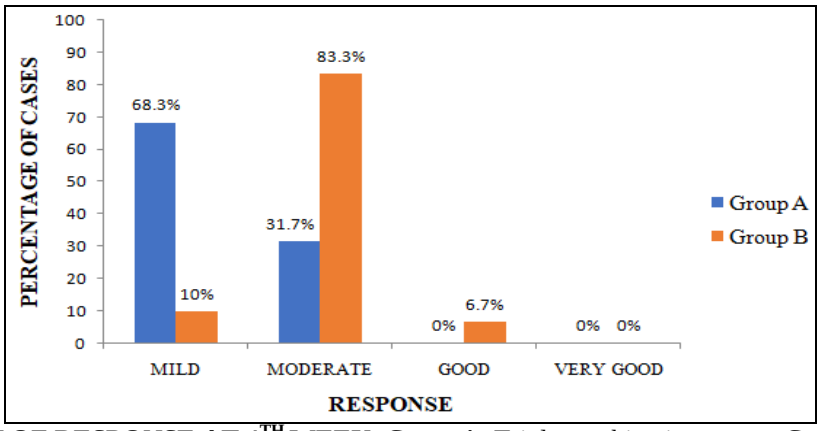

FIG. 3: COMPARISON OF RESPONSE AT 4TH WEEK. Group A: Triple combination cream; Group B: Triple combination cream + Tranexamic acid

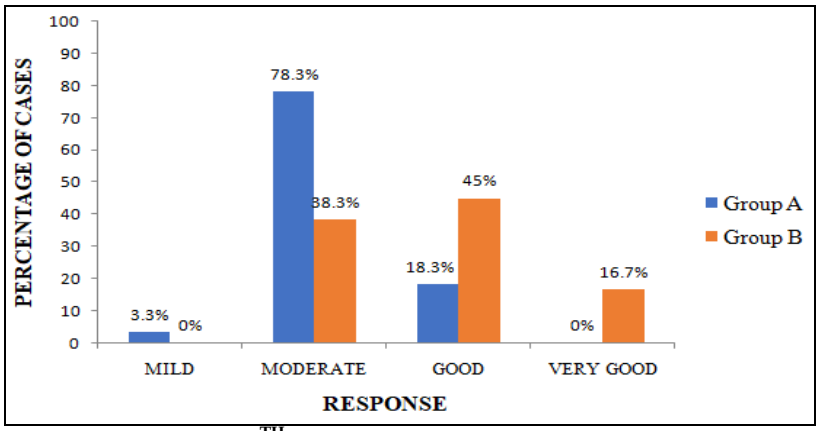

FIG. 4: COMPARISON OF RESPONSE AT 8TH WEEK. Group A: Triple combination cream; Group B: Triple combination cream + Tranexamic acid

When compared to group A, group B response was superior, and the results were significant with p <0.001. After eight weeks, the second follow-up revealed that 2 (3.3%) patients from group A showed mild response, 47 (78.3%) had a moderate response, and 11 (18.3%) had a good response. As shown in graph 4, group B showed moderate responses in 23 (38%) of cases, good responses in

27 (45%) cases, and very good responses in 10 (16.7%) of cases. In general, Group B outperformed group A with p-value of 0.0001 with significant results statistically.

Safety parameters, side effects seen among group B was erythema in 53 (88%) and Abdominal discomfort, gastritis among 09 (15%), and hypomenorrhea among 06(10%) of cases are other minor side effects.

Among group A, the common adverse effects were erythema in 6(10%) of instances and burning in 11(18%) of cases. Clotting factors were normal in both the groups and there were no visual defects too in any of the follow-up **Table 4.**

TABLE 4: SIDE EFFECTS

Side Effects	Group A		Group B		p value*
	No.	%	No.	%	
Erythema	6	10	53	88	0.0001
Burning	11	18	9	15	0.624
GI Symptoms	0	0	11	18	0.0001
Hypo menorrhea	0	0	6	10	0.012

*****Chi square test and Fischer-exact test.

DISCUSSION: Human melanogenesis malfunction causes melasma, a hyperpigmentation disorder that causes localized, acquired chronic hyper melanosis of skin. Our study evaluated tranexamic acid as a novel therapeutic agent targeting plasminogen [3].

According to our study, melasma occurred commonly between 31-40 years in about 56.66% cases, as mentioned in another study of Mushtaq S *et al,* where 33.74 ± 6.67 years was the common age group of melasma [14]. Among 120patients recruited patients there was an obvious female predominance comparable to study conducted by Agrawal M *et al* [15]. The reproductive age group was the most commonly affected, as 96.66% of them were married, between the ages of 30 and 39, and in almost 40% of instances, melasma began during pregnancy. In concurrence with the study of Krupa Shankar *et al.,* were, 257 out of 331 melasma patients were married [16]. One more study of Ortonne *et al.* stated that throughout the last trimester of pregnancy, the levels of all the reproductive hormone of placenta, ovary and pituitary increase. Wherein an increase in melanocyte-stimulating hormones, estrogen, and progesterone, as well as an increase in the transcription of tyrosinase and dopachrome tautomerase, stimulates melanogenesis [17]. About 38.33% of cases in the current study showed a positive first-degree correlation with family history, which is comparable to a multicentre study of Krupa Shankar *et al.* that found 31.1% of study participants had a family history [16] and a study by Agrawal M *et al.* that found 65% of positive correlation [15]. The present study highlights the chronic nature of melasma, as reflected by the duration of the condition among participants. This is comparable to another research of Krupa Shankar *et al,* in which 43% cases of melasma chronicity were for <3 years and 39.1% cases showed >3 years of chronicity [16]. The incidence of melasma and exacerbation of existing lesions were strongly associated with sun exposure in our study, similar to a results of Pawar S *et al,* where 100% correlation between sun exposure and melasma [18]. However, only around 55.12% cases indicated a favourable correlation in a Achar *et al* study [19].

Dermal was the common type seen, epidermal and mixed type were the next common according to our study, which was comparable to Achar *et al* study, in which 54.5% were dermal, 21.5% cases were epidermal and mixed constituted 24.1% [19]. Contrast results were seen in Iram Qazil *et al* study, where, epidermal (64%) was the common and next was mixed (24.1%) and the dermal type (14.3%).[14] A study by Agrawal M *et al,* the common pattern was Centro-facial in 70% cases [15]. The decreased in mean MASI score from start of study to fourth and eighth week was very clearly, better among group B. From the first follow-up itself, group B had better and faster responses with statistically significant results compared to group A in the present research. In comparison to a study by Padhi T *et al,* where oral tranexamic acid (250mg) plus fluticasone containing TCC against fluocinolone containing TCC alone was used. These results also showed tranexamic acid containing class showed early, sustainable results compared to TCC alone

and p-value were significant at fourth and at eight weeks [20]. According to another study by Krupa Shankar *et al.* which is based on evidence, fluorinated steroids, such as fluticasone and fluocinolone, are more effective and well tolerated than other strong steroids, such as mometasone or betamethasone. Fluticasone containing TCC was thus employed in our investigation [21]. According to Hyun Jung KIM *et al.*, tranexamic acid both by itself and in combination with other drugs, showed better MASI score with fewer and less frequent side effects, such as low GI discomfort, irritation of skin for transient period and hypomenorrhea [22].

The majority of the group B participants experienced erythema as the most frequent side effect in our study, while the group A experienced erythema only in 10% of cases and burning in 18.3% cases. Similar study by Karn *et al.* also showed that modest doses of TXA were safe and very effective to treat melasma as there was no major systemic side effects and minor once included burning sensation and erythema. [8]According to a different study of Hyun Jung KIM *et al.*, TXA occasionally caused adverse effects such moderate abdominal pain, temporary skin irritation, and hypomenorrhea [22].

Limitations: The present study only lasted eight weeks based on our pilot study were all the study subjects could follow-up till 2 months and later months we experienced too much dropouts. Long-term studies to evaluate the recurrence rates and optimal dosing of TXA are suggested for future studies.

CONCLUSION: While fluticasone-based TCC produced favorable initial results, it was less effective in sustaining the response compared to the TCC+TXA group. However, the rate of response increased more quickly and steadily when tranexamic acid was added to a triple combination. Based on the above-mentioned findings, TXA combined with TCC demonstrates greater efficacy and safety than TCC alone in reducing MASI scores in melasma patients.

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