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A Comparative Study of Efficacy between Oral Tranexamic Acid with Fluocinolone-Based Triple Combination Cream Versus Fluocinolone-Based Triple Combination Cream Alone in Melasma

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Abstract **Original Research Article**

Introduction: Melasma is an acquired, chronic, recurrent hyper-pigmentary disorder characterized by symmetric light-brown to bluish-gray macules and patches with irregular, sharp borders. The term "melasma" is derived from the Greek word "melas," meaning black, while "chloasma" refers to its occurrence during pregnancy, derived from "chloazein," meaning green. Clinically, melasma predominantly affects the face, including the forehead, cheeks, temples, upper lip, chin, and nose. ***Methods:*** This cross-sectional study was conducted on 60 clinically diagnosed cases of melasma attending the Skin and VD outpatient department of Combined Military Hospital (CMH), Dhaka, Bangladesh from January 2020 to June 2020. ***Result:*** Ages of the patient at onset of melasma, in majority (56.67%) cases were between 20-25 years and 90% study population was female. Most (56.67%) of the patients were housewife. Regarding the distribution of melasma 50% were found malar, 46.67% centro-facial and 3.33% mandibular. By 12 weeks, Group A's mean MASI score further reduced to 6.995 ± 6.056, and Group B's score decreased significantly to 2.19 ± 2.378. The P value of 0.00 confirms a statistically significant difference between the groups at 12 weeks. ***Conclusion:*** In conclusion, our study demonstrates that oral tranexamic acid in combination with fluocinolone-based triple combination cream is significantly more effective in treating facial melasma than the cream alone.

Keywords: Melasma, hyper-pigmentary disorder, tranexamic acid, fluocinolone, ultraviolet radiation.

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INTRODUCTION

Melasma is an acquired, chronic, recurrent hyper-pigmentary disorder characterized by symmetric light-brown to bluish-gray macules and patches with irregular, sharp borders [1]. The term "melasma" is derived from the Greek word "melas," meaning black, while "chloasma" refers to its occurrence during pregnancy, derived from "chloazein," meaning green. Clinically, melasma predominantly affects the face, including the forehead, cheeks, temples, upper lip, chin, and nose [2]. Less commonly, it may appear on the extensor arms and sternal region. Though considered a benign condition, melasma can significantly impact self-image and self-esteem, negatively affecting patients' quality of life [1,2].

Melasma affects approximately 5-6 million individuals in the United States, though its global prevalence is not well documented [3]. It occurs in both sexes and across all races and ages, though it is most common among women of reproductive age. Men constitute less than 10% of all melasma cases [3]. The condition is more prevalent among darker-skinned individuals with Fitzpatrick skin types IV to VI, particularly in regions with high ultraviolet radiation (UVR) intensity. It is frequently observed in Hispanic, Asian, and Afro-descendant populations. The typical age of onset ranges from 30 to 55 years, with rare occurrences during puberty or post-menopause [4,5].

The pathogenesis of melasma is multifactorial, involving genetic, hormonal, and environmental factors [6]. UVR is a primary aggravating factor, stimulating melanocytes and increasing melanin production. Hormonal influences, such as those from pregnancy, oral contraceptives, and hormone replacement therapy, also play significant roles in melasma development. Additionally, certain cosmetics and phototoxic drugs can exacerbate the condition [7].

Histologically, melasma is characterized by increased melanin deposition in the epidermis and/or dermis [8]. The condition is often classified into three

types based on Wood's lamp examination: epidermal, dermal, and mixed. Epidermal melasma shows enhanced pigmentation under Wood's lamp, while dermal melasma does not. Mixed melasma displays both patterns. Increased vascularization and solar elastosis are also noted in some cases, suggesting the involvement of dermal changes in its pathogenesis [9].

The treatment of melasma remains challenging due to its recurrent nature and multifactorial etiology. Traditional treatment modalities include topical depigmenting agents, chemical peels, laser therapy, and sun protection [10]. The most commonly used depigmenting agents are hydroquinone, retinoids, and corticosteroids, either alone or in combination. Triple combination creams, typically containing hydroquinone, tretinoin, and fluocinolone acetonide, are widely regarded as the gold standard treatment due to their synergistic effects on melanin synthesis and skin turnover [11].

Recently, oral tranexamic acid has emerged as a promising treatment for melasma. Tranexamic acid, a synthetic derivative of lysine, inhibits plasminogen activation and decreases the production of prostaglandins and arachidonic acid, which are implicated in melanogenesis [12]. Several studies have demonstrated the efficacy of oral tranexamic acid in reducing melasma severity, either as monotherapy or in combination with topical agents [13].

Melasma significantly impacts the quality of life due to its chronic and recurrent nature and its prominent localization on the face [14]. Patients often experience emotional distress, low self-esteem, and social stigma. The psychological burden can be substantial, leading to anxiety, depression, and social withdrawal. The visible nature of the condition and its association with cosmetic disfigurement contribute to the negative psychosocial impact [15].

OBJECTIVE

The objective of this study was to evaluate efficacy and side effects of Triple combination agents for the treatment of facial melasma.

METHODOLOGY & MATERIALS

This cross-sectional study was conducted on 60 clinically diagnosed cases of melasma attending the Skin and VD outpatient department of Combined Military Hospital (CMH), Dhaka, over a period of 24 weeks from January 2020 to June 2020. Patients aged 18 years and older, diagnosed with melasma, and willing to provide informed consent were included, while those with hypersensitivity to fluocinolone-based triple combination cream or tranexamic acid, pregnant or breastfeeding women, and those using other treatments for melasma within the last 6 months were excluded. Patient data were recorded on a pre-designed case record form, including the history of melasma regarding duration, relation to pregnancy, oral contraceptive use, drug history, and previous use of triple combination agents. The 60 patients were randomly separated into two groups. Group A patients were advised to apply the triple combination cream alone at night, while Group B patients were advised to take oral tranexamic acid twice daily in addition to applying the fluocinolone-based triple combination cream at night. The efficacy of the treatments was evaluated using the Melasma Area and Severity Index (MASI) score as proposed by Kimbrough-Green *et al.*, At each visit, side effects in the treatment area were determined. Statistical analysis was performed using appropriate software, with data expressed as mean ± standard deviation (SD) or as frequencies and percentages. Comparisons were made using t-tests or chi-square tests, with a p-value of <0.05 considered statistically significant. The study protocol was approved by an institutional review board, and informed consent was obtained from all patients prior to participation.

RESULT

Table 1: Distribution of age of the patient at onset (n=60)

Age in years	Number of patients	Percentage (%)
20-25	34	56.67
26-30	17	28.33
31-35	6	10%
36-40	3	5%

Table 1 presents the distribution of age at onset among 60 patients diagnosed with melasma. The majority of cases (56.67%) began between the ages of 20 and 25 years, indicating a significant incidence during early adulthood. A notable proportion (28.33%) reported onset between ages 26 and 30 years, suggesting continued susceptibility in the late twenties. A smaller subset (10%) experienced onset between ages 31 and 35 years, while the least common age group for onset was 36 to 40 years, comprising only 5% of the patients.

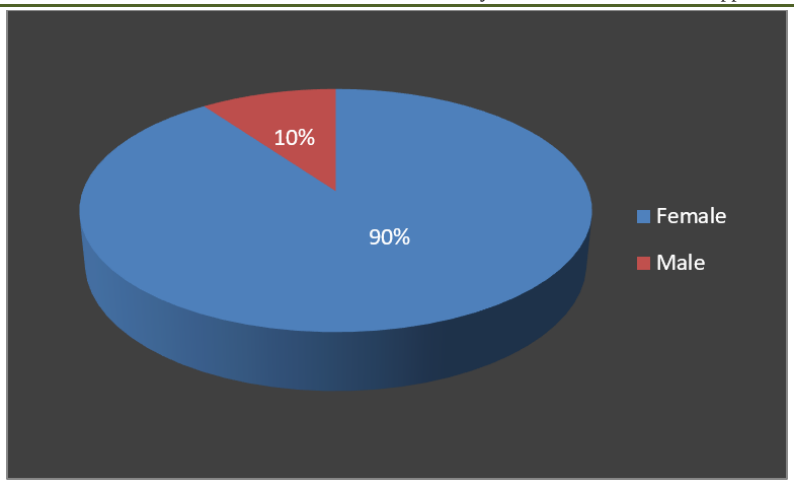

Figure 1: Gender distribution of our study patients (n=60)

Based on Figure 1, which depicts the gender distribution of the study patients (n=60), it is evident that the majority of the patients are female. Specifically, 54 patients (90%) are female, while only 6 patients (10%) are male.

Table 2: Distribution of occupation (n=60)

Occupation	Number of patients	Percentage (%)
Housewife	34	56.67
Student	13	21.67
Service holder	10	16.67
Buisness	3	5.0

Analyzing Table 2, it is observed that the majority of patients (56.67%) are housewives, indicating a higher prevalence of melasma among this group. Students comprise 21.67% of the patients, followed by service holders at 16.67%. The least represented group is business persons, accounting for only 5.0% of the patients.

Table 3: Distribution of types of melasma (n=60)

Distribution	Number of patients	Percentage (%)
Centro-facial	28	46.67
Malar	30	50.0
Mandibular	02	3.33

Table 3 demonstrates the distribution of different types of melasma among the study patients. The most common type is malar melasma, affecting 50.0% of the patients. Centro-facial melasma is also prevalent, observed in 46.67% of the patients. Mandibular melasma is the least common, accounting for only 3.33% of the cases. This distribution indicates that malar and centro-facial melasma are the predominant forms, suggesting a need for targeted treatments for these specific types.

Table 4: Melasma area severity index-comparison between Group A and Group B at baseline, 4 weeks and 12 weeks

Group	Mean MASI at 0 weeks	P value	Mean MASI at 4 weeks	P value	Mean MASI at 12 weeks	P value
Group A	15.425±1.09	0.883	11.075±9.167	0.014	6.995±6.056	0.00
Group B	18.243±1.05		6.135±4.94		2.19±2.378	

Table 4 compares the Melasma Area Severity Index (MASI) scores between Group A and Group B at baseline, 4 weeks, and 12 weeks. At baseline (0 weeks), the mean MASI score for Group A was 15.425 ± 1.09, and for Group B, it was 18.243 ± 1.05. The P value of 0.883 indicates no statistically significant difference between the groups at the start of the study. After 4 weeks, the mean MASI score for Group A decreased to 11.075 ± 9.167, while Group B's score dropped to 6.135 ± 4.94. The P value of 0.014 suggests a statistically significant difference between the groups at this point. By 12 weeks, Group A's mean MASI score further

reduced to 6.995 ± 6.056, and Group B's score decreased significantly to 2.19 ± 2.378. The P value of 0.00 confirms a statistically significant difference between the groups at 12 weeks.

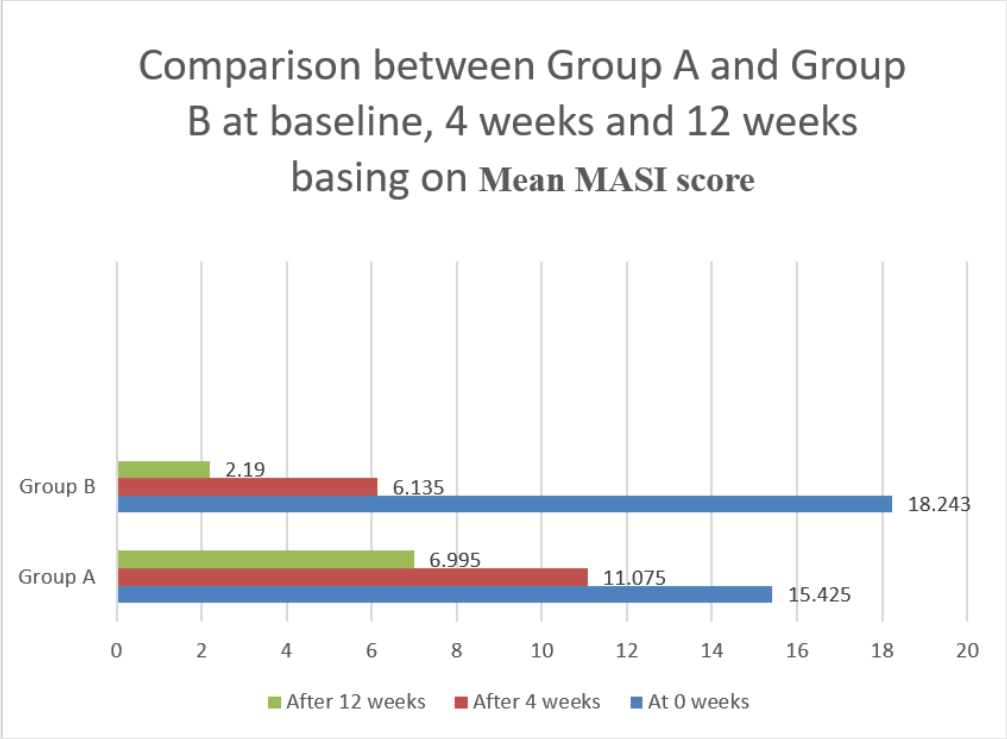

Figure 2: Comparison between Group A and Group B at baseline, 4 weeks and 12 weeks basing on Mean MASI score

Figure 2 depicts the trend of the Mean MASI scores for Group A and Group B at baseline, 4 weeks, and 12 weeks. The data shows a greater reduction in MASI scores for Group B, highlighting the efficacy of combining oral tranexamic acid with fluocinolone-based triple combination cream compared to using the cream alone.

Table 5: Comparison of adverse effects among both groups

Adverse effects	Present in number of patients			
	Group A		Group B	
Erythema	4	13.3%	3	10%
Burning	3	10%	2	6.67%
Hypopigmentation	0	0	3	10%
Oligomenorrhoea	0	0	2	6.67%
Other systemic side effects	0	0	1	3.33%

Table 5 provides a comparison of adverse effects experienced by patients in Group A and Group B. In Group A, erythema was present in 4 patients (13.3%), burning in 3 patients (10%), and no cases of hypopigmentation, oligomenorrhoea, or other systemic side effects were reported. In Group B, erythema was present in 3 patients (10%), burning in 2 patients (6.67%), hypopigmentation in 3 patients (10%), oligomenorrhoea in 2 patients (6.67%), and other systemic side effects in 1 patient (3.33%). This comparison highlights that while both groups experienced some adverse effects, Group B had additional cases of hypopigmentation, oligomenorrhoea, and other systemic side effects not seen in Group A.

DISCUSSION

This cross-sectional study was conducted among patients visiting the Dermatology and Nephrology departments at Dhaka CMH from January 2020 to June 2020. Patients were randomly selected and divided into two groups. This study aimed to evaluate the efficacy and side effects of oral tranexamic acid in combination with fluocinolone-based triple combination cream for treating facial melasma compared to fluocinolone-based triple combination cream alone, assessed using the Melasma Area and Severity Index (MASI) score.

Melasma is a common pigmentary disorder that presents as symmetric hyperpigmented macules, predominantly on the face. The pathogenesis of melasma is multifactorial, involving genetic predisposition, ultraviolet radiation exposure, hormonal influences, and certain medications. Fitzpatrick *et al.,* described melasma as a condition characterized by light microscopic, ultrastructural, and immunofluorescence findings, highlighting its complex etiology [1]. Hexsel *et al.,* further emphasized the hormonal component by reporting a high prevalence of melasma during pregnancy [2]. Ebrahimi and Naeini explored the potential of topical tranexamic acid as a treatment, opening the door for oral administration investigations [3].

The age of onset of melasma in our study was predominantly between 20 to 25 years (56.67%). This contrasts with the findings of Patil and Deshmukh, who reported that the most common age group was 31 to 40 years (45%), with the second most common group being 18 to 30 years (42%) [16].

Gender distribution in our study revealed that 90% of the patients were female, while 10% were male. This is similar to the findings of Zell, who reported a high prevalence of melasma among females [17]. Sen *et al.,* also found a female predominance in their study, with 60% female and 40% male participants [18].

Regarding the distribution of melasma, our study showed that 50% of patients had malar distribution and 46.67% had centro-facial distribution. These findings are similar to those of Leenutaphong *et al.,* who observed that 47% of patients had malar distribution and 43% had centro-facial distribution [19].

In terms of occupation, most of the patients in our study were housewives (56.67%), which is similar to the study conducted by Sarkar *et al.,* They found that 60% of their patients were housewives, 30% were students, and 10% were businessmen [20].

Melasma Area Severity Index (MASI) scores between Group A and Group B at baseline, 4 weeks, and 12 weeks. At baseline (0 weeks), the mean MASI score for Group A was 15.425 ± 1.09, and for Group B, it was 18.243 ± 1.05. The P value of 0.883 indicates no statistically significant difference between the groups at the start of the study. After 4 weeks, the mean MASI score for Group A decreased to 11.075 ± 9.167, while Group B's score dropped to 6.135 ± 4.94. The P value of 0.014 suggests a statistically significant difference between the groups at this point. By 12 weeks, Group A's mean MASI score further reduced to 6.995 ± 6.056, and Group B's score decreased significantly to 2.19 ± 2.378. The P value of 0.00 confirms a statistically significant difference between the groups at 12 weeks.

Adverse side effects noted throughout the study included erythema (13.3% in group A and 10% in group B), burning sensation (10% in group A and 6.67% in group B), hypopigmentation (10%), oligomenorrhoea (6.67%), and other systemic side effects (3.33%) in group B patients. These findings are consistent with the observations of Torok *et al.,* who reported similar side effects with triple combination cream use [21]. Ferreira Cestari *et al.,* also noted these adverse effects in their study comparing triple combination cream and hydroquinone 4% cream [22].

Limitations of the study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

In conclusion, our study demonstrates that oral tranexamic acid in combination with fluocinolone-based triple combination cream is significantly more effective in treating facial melasma than the cream alone. This combined therapy offers a promising approach to managing melasma, with a substantial improvement in MASI scores and a tolerable side effect profile. Further large-scale studies are needed to confirm these findings and to establish standardized treatment protocols for melasma.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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