ORIGINAL ARTICLE

EFFICACY OF ORAL TRANEXAMIC ACID VERSUS PLACEBO IN THE TREATMENT OF EPIDERMAL MELASMA

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Background: Epidermal melasma, a common hyperpigmentation disorder, can cause significant psychological and social distress. This study aimed to evaluate the efficacy of oral tranexamic acid (TXA) in treatment of epidermal melasma. **Methods:** This cross-sectional study was conducted at the Dermatology Department, PIMS, Islamabad, from Oct 2020 to Apr 2021. A total of 202 patients aged 13–60 years with epidermal melasma for at least six months, and a Melasma Area and Severity Index (MASI) score of 20–36, were randomly assigned to two groups. Group A received oral TXA (250 mg twice daily), while Group B received a placebo. Patients were assessed at four-week intervals, with final evaluation at 12 weeks. Statistical comparisons were performed using *t*-tests and Chi-square tests. **Results:** At three months, the mean MASI reduction was significantly greater in Group A (22.6±8.1) than in Group B (13.7±6.6, p=0.001), with a higher mean percent reduction in Group A (60.2±20.3 *vs* 37.7±19.5%), (p=0.001). An excellent or good response was observed in 67.3% of Group A patients compared to 21.8% in Group B (p=0.001). **Conclusion:** Oral TXA significantly reduced MASI scores compared to placebo, demonstrating superior efficacy in improving epidermal melasma.

Keywords: Efficacy, Epidermal Melasma, MASI score, Placebo, Tranexamic Acid, Treatment

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INTRODUCTION

Melasma is a frequently encountered disorder characterised by the development of pigmentation on the face. It tends to appear in a symmetrical pattern and is more commonly observed in females and individuals with darker skin tones.[1,2] The condition is distinguished by irregular dark brown spots and patches, primarily appearing on parts of the skin that are exposed to sunlight, particularly the face.[3] The exact cause of this condition is not fully comprehended, however, it is widely acknowledged that hyperactive melanocytes, stimulated by ultraviolet light, are the primary factor. Additional considerations encompass genetic predisposition, hormone-based treatment, photo-sensitizing medications, and the state of being pregnant.[4] Melasma is categorised as dermal, epidermal, or mixed types, according on the level at which the pigment is located. Given its aesthetically unappealing appearance, melasma can lead to substantial psychological and social difficulties, emphasising the importance of therapy.[5,6]

The standard treatment usually consists of using a sunscreen that protects against a wide range of ultraviolet rays, along with depigmenting substances such as hydroquinone, azelaic acid, retinoic acid, kojic acid, and different natural plant extracts including licorice root and mulberry extracts. Additional therapeutic options encompass chemical peels and laser treatments, which have the potential to induce irritation, post-inflammatory hyperpigmentation, contact dermatitis, or incur significant costs.[7,8] Tranexamic acid has been identified as a promising remedy for melasma. While the precise process is not yet understood, it is believed that it inhibits the interaction between melanocytes and keratinocytes, and has the potential to reverse the dermal alterations linked to enlarged blood vessels in melasma. Tranexamic acid is generally well tolerated with minimal side effects. However, at dosages over 500 mg/day, the adverse effects can become more noticeable.[6] These side effects may include oligomenorrhoea, deep vein thrombosis, and pulmonary embolism. It is important to note that no thromboembolic consequences have been documented with the modest doses of tranexamic acid used for treating melasma.[9]

While existing treatments can cause irritation and are often costly, tranexamic acid offers a potentially effective and well-tolerated alternative. This study aims to evaluate the efficacy of oral tranexamic acid versus placebo in treating epidermal melasma, providing new insights into its therapeutic potential and safety profile. By comparing it directly to a placebo, this research will add robust evidence to support its use and guide future clinical practices.

MATERIAL AND METHODS

With ethical committee approval (F.2-11/SZABMU/AS&RB-52/2018), the comparative cross-sectional study was conducted at the Dermatology OPD of PIMS,

Islamabad. After obtaining written informed consent, the size and severity of each melasma lesion were recorded.

The sample size was calculated using the WHO Sample Size Calculator based on the following parameters: a level of significance (α) of 5%, a power of test (1-β) of 90%, an anticipated efficacy of tranexamic acid (P1) of 0.49, and an anticipated efficacy of placebo (P2) of 0.27. This resulted in a total of 202 patients being enrolled in the study, with 101 patients in each group.[10] Inclusion criteria included patients of either gender, aged between 13 and 60 years, with a diagnosis of epidermal melasma that had been present for six months or more, and a baseline MASI score of 20–36. Exclusion criteria encompassed patients who had been using other melasma therapies within the past two months, pregnant or lactating patients, those taking oral contraceptive pills, individuals with a history of any endocrine disorder, patients with thromboembolic disorders, and those with a deranged clotting profile and PT/INR.

Patients were assigned to Group A (oral tranexamic acid capsule 250 mg BD) or Group B (similar-looking placebo capsule) using the lottery method. Complete blood profile and clotting profile were checked initially and monthly thereafter. Patients were instructed to apply broad-spectrum standardized sunscreens and discontinue any other therapies during the treatment period. Follow-ups were scheduled every 4 weeks to analyse changes in melasma, grading responses as excellent, good, fair, or poor. Final analysis was conducted after 12 weeks, with treatment considered efficacious if the response was excellent, good, or fair, and not effective if the response was poor.

Data were entered and analysed using SPSS-24. Mean and standard deviation were calculated for quantitative variables (age, MASI score at baseline and after treatment). Frequencies and percentages were calculated for qualitative variables (gender, efficacy). Efficacy between the tranexamic acid and placebo groups was compared using Chi-square test, with a $p \leq 0.05$ considered statistically significant.

RESULTS

There were 24 (23.8%) males and 77 (76.2%) females in the tranexamic acid (TXA) group, while the placebo group had 18 (17.8%) males and 83 (82.2%) females. Regarding age distribution, 77 (76.2%) patients in the TXA group and 90 (89.1%) patients in placebo group were aged between 19–40 years. In the 41–60 years age group, there were 24 (23.8%) patients in the TXA group and 11 (10.9%) patients in the placebo group. The mean age was 35.1±8.7 years for the TXA group and 33.7±5.1 years for the placebo group, with an overall mean age of 34.4±7.3 years. (Table-1).

In both groups, the mean MASI score at baseline was 37.9±6.1 for the tranexamic acid (TXA) group and 37.1±4.9 for the placebo group, with no significant difference between them (p=0.354). However, at months 1, 2, and 3, the MASI scores were significantly lower in the TXA group compared to the placebo group (p<0.001 for all). The mean change from baseline at 3 months was higher in the TXA group (22.6±8.1) than in the placebo group (13.7±6.6), with a significantly greater percent change from baseline in the TXA group (60.2±20.3) compared to the placebo group (37.7±19.5) (p<0.001 for both). (Table-2).

Response to therapy at 3 months differed significantly between the groups. In the tranexamic acid (TXA) group, 30.7% of patients had an excellent response, 36.6% had a good response, 26.7% had a fair response, and 5.9% had a poor response. Conversely, in the placebo group, only 9.9% had an excellent response, 11.9% had a good response, 48.5% had a fair response, and 29.7% had a poor response (p=0.001). (Table-3).

At 3 months, efficacy of treatment differed significantly between the groups. In the tranexamic acid (TXA) group, 67.3% of patients showed efficacy, whereas in the placebo group, only 21.8% showed efficacy (p=0.001). (Table-4).

At 3 months, efficacy of treatment stratified by gender showed significant differences between the groups. In males, 66.7% of those in the tranexamic acid (TXA) group and 33.3% in the placebo group showed efficacy (p=0.032). Similarly, in females 67.5% in the TXA group and 19.3% in the placebo group showed efficacy (p=0.001). (Table-5).

Table-1: Gender and age distribution in groups

Variables	TXA	Placebo	Total
Males	24 (23.8%)	18 (17.8%)	42 (20.8%)
Females	77 (76.2%)	83 (82.2%)	160 (79.2%)
19–40 Years	77 (76.2%)	90 (89.1%)	167 (82.7%)
41–60 Years	24 (23.8%)	11 (10.9%)	35 (17.3%)
Mean±SD Age (Years)	35.1±8.7	33.7±5.1	34.4±7.3

Table-2: MASI score at different times and change from baseline in both groups (*t*-test)

MASI Score Assessment	TXA	Placebo	*p*
Baseline	37.9±6.1	37.1±4.9	0.354
Month 1	30.1±5.8	33.2±4.9	<0.001
Month 2	23.8±6.7	28.2±6.4	<0.001
Month 3	15.2±8.4	23.4±8.4	<0.001
Change from Baseline at 3 Months	22.6±8.1	13.7±6.6	<0.001
Percent Change from Baseline at 3 Months	60.2±20.3	37.7±19.5	<0.001

Table-3: Response to therapy at 3 months in both groups (Chi-square) [n (%)]

Response Category	TXA	Placebo	Total	*p*
Excellent	31 (30.7)	10 (9.9)	41 (20.3)	<0.001
Good	37 (36.6)	12 (11.9)	49 (24.3)	
Fair	27 (26.7)	49 (48.5)	76 (37.6)	
Poor	6 (5.9)	30 (29.7)	36 (17.8)	

Table-4: Efficacy at 3 months in groups [n (%)]

Efficacy	TXA	Placebo	Total	*p*
Present	68 (67.3)	22 (21.8)	90 (44.6)	0.001
Absent	33 (32.7)	79 (78.2)	112 (55.4)	

Table-5: Efficacy at 3 months in both groups (stratification of gender) [n (%)]

Gender	Efficacy	TXA	Placebo	Total	*p*
Males	Present	16 (66.7)	6 (33.3)	22 (52.4)	0.032
	Absent	8 (33.3)	12 (66.7)	20 (47.6)	
Females	Present	52 (67.5)	16 (19.3)	68 (42.5)	0.001
	Absent	25 (32.5)	67 (80.7)	92 (57.5)	

DISCUSSION

Epidermal melasma presents a therapeutic challenge due to its chronic and recurrent nature. While various treatments exist, their efficacy and tolerability remain variable. This study investigates the efficacy of oral tranexamic acid versus placebo in managing epidermal melasma, aiming to provide evidence-based guidance for clinical practice. Tranexamic acid depigments via inhibiting plasmin activator. Preventing plasminogen binding to keratinocytes reduces free arachidonic acid, prostaglandins, melanocyte tyrosinase activity, and melanocyte-stimulating hormone. VEGF and endothelin-1 are also decreased. Besides this, tranexamic acid fights skin problems by reducing inflammation and allergies.[11,12]

Our study results are similar to Del Rosario E *et al*[10], who determined the efficacy of oral Tranexamic acid in patients with melasma of moderate to severe degree. Their results showed a 49% reduction in mMASI score in the TXA group versus 18% in the control group at 3 months of treatment. They further demonstrated that 3 months after treatment was stopped, there was a 26% reduction in mMASI score in the TXA group compared with the baseline visit versus a 19% reduction in the placebo group. Our study results are similar with an efficacy of 67.3% with TXA versus 21.8% in placebo group. We, however, did not monitor the patients further after 3 months.

Our study demonstrated a significantly higher mean change from baseline at 3 months in the TXA group (22.6±8.1) compared to the placebo group (13.7±6.6), with a notably greater percent change from baseline in the TXA group (60.2±20.3) versus the placebo group (37.7±19.5) (p<0.001 for both), consistent with Minni *et al*[13], where significant reductions in MASI scores were observed within each treatment group. Sarwar *et al*[14] demonstrated 40% reduction in melasma in patients on oral TXA supporting our findings.

Our study results corroborate with Batra *et al*[15] who observed good results in 25% and very good results in 70% cases on oral TXA. Colferai *et al*[16] demonstrated significant improvements in MASI scores, with the MELASQoL value increasing from 55.0 to 56.1 in their treatment group. Conversely, Del Rosario *et al*[10] reported a 49% reduction in mMASI score in the tranexamic acid group at 3 months, while our study showed a significantly higher mean change from baseline at 3 months in the TXA group compared to the placebo group, with a greater percent change. These findings collectively support the efficacy of oral tranexamic acid in improving melasma severity, highlighting its potential as a valuable therapeutic option for patients with this condition.

Our findings align with Mushtaq *et al*[17] where efficacy was observed in 67.3% of patients in the tranexamic acid group compared to 21.8% in the placebo group, indicating a significant improvement in melasma severity. Minni *et al*[13] reported a marked improvement in melasma with oral tranexamic acid treatment, with 65.6% of patients showing improvement compared to 27.1% in the placebo group after 12 weeks. Our study demonstrated a similar trend of efficacy with TXA treatment, showcasing its potential as a promising therapeutic option for melasma management. However, it's imperative to note the side effects observed, consistent with Minni *et al*[13] indicating the importance of monitoring adverse events with TXA therapy.

One limitation of the study is the absence of long-term follow-up to assess the durability of treatment response. However, a notable strength lies in the utilization of a randomized controlled trial design coupled with comprehensive statistical analysis.

CONCLUSION

MASI scores declined significantly over 1, 2, and 3 months in both groups, with lower scores in the oral tranexamic acid group compared to placebo. The mean absolute and percent decrease in MASI scores at 3 months, as well as the efficacy (excellent or good response), were significantly better in the TXA group.

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