Original Article

Topical 5% Tranexamic Acid in Melasma

Effectiveness of Topical 5% Tranexamic Acid in the Treatment of Melasma

Farhad Ali, Yamna Hassan, Humaira Wazir and Kashmala

ABSTRACT

Objective: To evaluate the efficacy and safety of topical 5% tranexamic acid in the treatment of moderate to severe melasma.

Study Design: Prospective interventional study

Place and Duration of Study: This study was conducted at the Department of Dermatology, Lady Reading Hospital, Peshawar, between November 6, 2021, and May 6, 2022.

Methods: After giving informed consent, 99 patients aged between 18 - 50 years of both genders with a clinically diagnosed moderate to severe melasma were enrolled. Topical 5% tranexamic acid cream, which was put daily in two applications during one week, was used to treat patients over 12 weeks, as well as to use broad-spectrum sunscreen (SPF 50+). The effectiveness of the treatment was measured by the Melasma Area and Severity Index (MASI) score at baseline and week 12. Physician Global Assessment (PGA) and patient satisfaction were taken as secondary outcomes. Safety was assessed by conducting clinical check-ups and reporting of adverse events.

Results: The mean age of participants was 32.25 ± 9.65 years, with a female predominance (57.6%). Overall clinical effectiveness was observed in 63 patients (63.6%) following 12 weeks of treatment. No statistically significant association was found between treatment response and age (p=0.61), gender (p=0.90), or disease duration (p=0.27). Topical tranexamic acid was well tolerated, and no major adverse effects were reported during the study period.

Conclusion: Topical 5% tranexamic acid is an effective and safe treatment option for moderate to severe melasma. Its favorable efficacy, good tolerability, and lack of significant influence by demographic or disease-related factors make it a useful therapeutic alternative in routine clinical practice.

Key Words: Melasma, Tranexamic acid, Topical therapy, MASI score, Hyperpigmentation

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INTRODUCTION

Melasma is an acquired, non-progressive, skin condition that is hyperpigmentary, symmetrical, irregular brown to gray-brown macules and patches of the sun-exposed skin, mostly the face. It predominates in Fitzpatrick skin phototypes III-V, and its prevalence is heavily higher in women, with a high burden in terms of psychology, usually reducing the quality of life as it is chronic, relapsing, and treatment-resistant[1,2]. The pathogenesis is complex, and it comprises genetic predisposition, ultraviolet (UV) radiation, visible light, hormonal factors, and vascular elements, all of which trigger melanogenesis and heighten activity in melanocytes[3]. The traditional first-line treatments are directed at the melanin production and transfer and encompass topical agents like hydroquinone, retinoids, corticosteroids and their combination[4]. They are, however, often constrained by concerns on skin irritation, ochronosis (especially with long-term hydroquinone) and a high incidence of recurrence when stopped. This has resulted in a need to have safer, well-tolerated, and effective therapeutic alternatives[5].

A synthetic derivative of lysine amino acid, tranexamic acid (TXA) has become a promising agent. Its original therapeutic use as an antifibrinolytic systemically has been shown to have applications in melasma due to its inhibition of plasminogen activation, consequently lowering the relationship between keratinocytes and melanocytes, by reducing arachidonic acid and alpha-melanocyte-stimulating hormone (alpha-MSH) levels[6]. It is also hypothesized to counter UV-induced melanogenesis by disrupting platelet-activating factor receptor pathway and inhibit angiogenesis to cover the vascular aspect that is becoming more important in melasma.

Although oral tranexamic acid has shown high effectiveness, its application is moderated by the fact

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that it carries strong side effects on the body with the most infamous being the possibility of promoting thromboembolic occurrences, thus it requires selective use of patients and restricting its unlimited use[7,8]. This has raised significant curiosity about topical preparations as a method of administering the medicine specifically to the target skin and reducing the systemic absorption and other risks. Topical TXA, especially at 5% has been studied, with initial research indicating that it has the capacity to reduce the weight of melasma by inhibiting a range of pathways in its pathogenesis, with a less adverse profile than its oral counterpart[9,10].

The main Aim of the proposed study is to compare the clinical efficacy and safety of topical 5 percent tranexamic acid in the management of moderate to severe facial melasma. This involves measuring the level of pigment lightening, increase in melasma area and severity index (MASI) scores, patient satisfaction, and observation of local or systemic adverse effects of any kind within a stipulated treatment period. Our hypothesis is that topical 5% TXA will be an effective and well-tolerated therapeutic modality, and it will be a valuable addition to the existing armamentarium in dealing with this difficult dermatological condition.

METHODS

This prospective interventional study was carried out at the Department of Dermatology, Lady Reading Hospital, Peshawar, between November 6, 2021, and May 6, 2022. The study was approved by the Institutional Review Board of the hospital, and the informed consent of all participants was obtained in writing before study enrollment.

A total of 99 patients aged 18-50 years, both sexes, with clinically diagnosed moderate to severe melasma (of symmetrical or asymmetrical distribution) were included. The exclusion criteria were pregnancy, lactation, taking oral contraceptive pills, known hypersensitivity to tranexamic acid, and a history of major systemic diseases (e.g., myocardial infarction, chronic kidney disease) that may conflict with taking the study medication or result in follow-up.

The participants were all given a topical 5% tranexamic acid cream and told to apply it to the entire affected part of their face in a thin layer 2 times per day (morning and evening). The patients were expected to apply a broad-spectrum sunscreen (SPF 50 or higher) to their face every morning and were told not to use any other topical depigmenting product, or a procedure to treat melasma over the course of the study.

The first efficacy outcome was the change in the severity of melasma which was measured by the Melasma Area and Severity Index (MASI) score. A single dermatologist was asked to determine the MASI score at baseline (week 0) and at the last visit (week 12) to limit the effect of inter-observer variability. Secondary outcomes were Physician Global Assessment (PGA) of improvement (graded out of 5 points) and patient satisfaction, which was measured by the use of a structured questionnaire (5-point Likert scale) at the treatment end. The safety was assessed by direct clinical examination and patient adverse events (e.g, erythema, irritation, burning, peeling) at every visit.

Statistical software SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyze the statistics. The Shapiro-Wilk test was used to determine the normality of data. The continuous variables were reported in the form of mean ± standard deviation, and the categorical variables were reported in terms of frequencies and percentages. Paired-sample t-test (in case of normally distributed data) or Wilcoxon signed-rank test (in case of non-parametric data) was conducted on the difference between the MASI score at the baseline and week 12. The value of $p < 0.05$ was taken as significant. The sample size was calculated to be 99 to give power of 80% to identify a clinically meaningful change in MASI score (effect size 0.5) at a two sided alpha level of 0.05, using past studies of topical tranexamic acid in melasma.

RESULTS

The research sample involved 99 patients with moderate to severe melasma. The average age of the study subjects was 32.25 years with a standard deviation of 9.65, and the average length of illness was 3.67 months with a standard deviation of 1.70 months. Most of the patients (54.5, n=54) fell within the age group of 16 and 30 years. The female dominance was predominant as 57 female (57.6) and 42 male (42.4) participants were included (Table 1).

Table No. 1: Baseline Demographic and Clinical Characteristics (n=99)

Characteristic	**Mean ± SD / Frequency (%)**
Age (Years)	32.25 ± 9.65
Duration of disease (months)	3.67 ± 1.70
Age Distribution	
16 - 30 years	54 (54.5%)
31 - 40 years	23 (23.2%)
41 - 50 years	22 (22.2%)
Gender	
Male	42 (42.4%)
Female	57 (57.6%)

Topical treatment with 5% tranexamic acid was proved to be clinically effective on 63 patients which resulted in an overall effectiveness rate of 63.6% (Figure-1).

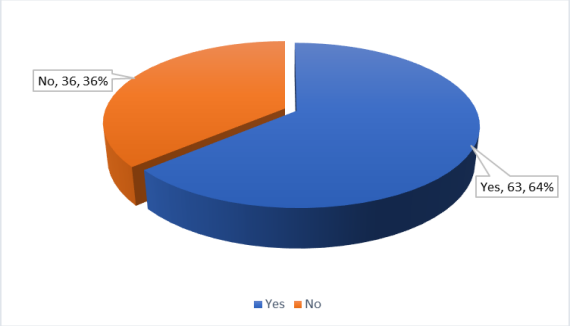

Figure No. 1: Overall effectiveness of topical 5% Tranexamic Acid

Subgroup analysis was conducted on the effect of age, gender and disease duration on the response to treatment. The rate of effectiveness in the various age groups was 50.8% (16-30 years), 25.4% (31-40 years), and 23.8% (41-50 years). Statistical results indicated that there was no significant correlation between the effectiveness of the treatment and age (p=0.60). Table-2.

Equally, there was no marked gender disparity in response (p=0.90), and the effectiveness rates of 42.9% in males and 57.1% in females were found. Table-3.

The time taken with disease was also not a predictive factor (p=0.61) because efficacy was similar in patients with disease duration of 1-3 months (41.3%) and those with disease duration of more than 3 months (58.7%). Table 4.

Table No. 2: Effectiveness stratified by age group

Age Group	Effective, n/N (%)	Not Effective, n/N (%)	p-value
16 - 30 years	32/54 (59.3)	22/54 (40.7)	0.610
31 - 40 years	16/23 (69.6)	7/23 (30.4)	
41 - 50 years	15/22 (68.2)	7/22 (31.8)	
χ^2 test for independence.			

Table 3: Effectiveness stratified by gender

Gender	Effective, n/N (%)	Not Effective, n/N (%)	p-value
Male	27/42 (64.3)	15/42 (35.7)	0.906
Female	36/57 (63.2)	21/57 (36.8)	
χ^2 test with Yates' correction.			

Table No. 4: Effectiveness stratified by disease duration

Duration	Effective, n/N (%)	Not Effective, n/N (%)	p-value
1 - 3 months	26/45 (57.8)	19/45 (42.2)	0.269
> 3 months	37/54 (68.5)	17/54 (31.5)	
χ^2 test.			

DISCUSSION

Melasma is a recurring and persistent pigmentary disease, which can be a therapeutic challenge due to its multifactorial etiology and a high recurrence rate. Tranexamic acid (TXA), the antifibrinolytic agent has received growing interest in recent years because of its abilities to inhibit the ultraviolet induced plasmin activity in the keratinocytes leading to an inhibition in melanocyte activation and synthesis of melanin. The current study tested the effectiveness of topical 5% tranexamic acid in individuals with moderate and severe melasma and showed a positive clinical response in almost two-thirds of the study population.

An overall effectiveness rate of 63.67% was found at 12 weeks of the treatment in the present study. The result is widely in line with other studies that have been published to evaluate topical TXA on melasma. Sim et al found that topical tranexamic acid showed significant improvement on MASI scores, with clinical response rates of 55 70, based on baseline severity and treatment duration[11]. Similarly, another study reported significant reduction of MASI score using topical TXA which proved the effectiveness of topical TXA as a depigmenting agent. The similarity in efficacy levels in these studies could be due to the similar concentration of TXA, treatment time and the instruments used to measure the outcome especially the MASI scoring.

The age of patients in this study (32.25 ± 9.65 years) and the predominance of female (57.6%) are in line with the epidemiological profile of melasma that is published in the literature. Multiple studies have observed that the occurrence of melasma is higher among women of reproductive age, probably due to hormonal factors, ultraviolet radiation and genetic factors. The marginally reduced female preponderance in the current study relative to certain international reports could be attributable to regional sociocultural influences, the amount of sun exposure that men have

to at work, and the healthcare-seeking attitude among the locals.

The stratified analysis did not show any statistically significant relationship between the response to treatment and age, gender or duration of the disease. These results align with the results of Srishti et al[12] who found that response to TXA therapy was not dependent on demographic factors. Other authors have however indicated that shorter period of illness might have a positive outcome because there will be reduced dermal melanophages and vascular involvement[13]. The absence of a meaningful connection in the current study, may be due to the relativity of the period of the disease among the subjects and the small size of the sample, which may have been too small to detect the slightest differences between subgroups.

Topical application of TXA was highly acceptable in this study and none of the significant adverse effects were reported. This safety profile is in line with previous works which have indicated the benefit of topical TXA compared to oral preparations which have theoretical risk of thromboembolism. Bagherani et al[14] have also highlighted that topical application offers localized action and has low systemic absorption, thus indicating that it is an appropriate choice of long-term management specifically in patients whose systemic therapy is contraindicated.

Tranexamic acid has a clear mechanism of action over other topical agents that have been used traditionally to treat melasma, such as hydroquinone, retinoids and corticosteroid combinations as well as a reduced side effect profile including irritant dermatitis, ochronosis, and rebound hyperpigmentation[15]. Despite the fact that triple-combination therapy is the gold standard in most of the guidelines, recent comparative studies indicate that TXA could be especially efficient in patients who are not able to tolerate hydroquinone, or as an adjunction with the purpose to increase and sustain therapy response[16]. The disparity in reported efficacy of TXA and conventional depigmenting agents between studies could be due to differences in formulation, adherence, sun protection habits and severity baseline.

Despite its favourable results, the current study has some limitations which must be taken into consideration. The lack of a control or comparator group restrains the direct attribution of improvements observed to tranexamic acid only, but using sunscreen by all participants is a measure that indicates actual real-life clinical practice. Further, the comparatively brief follow-up period does not allow any evaluation of long-term response and recurrence rates as it is clinically important in melasma. Randomized controlled studies involving larger samples, extended follow-up, and direct comparison with recognized treatment should be conducted in the future to further clarify the place of topical TXA in the treatment of melasma.

CONCLUSION

This research has shown that topical 5% tranexamic acid is a safe and effective treatment method to be used in the management of moderate to severe melasma. It has been found that almost two-thirds of patients showed a clinically significant improvement in response to 12 weeks of treatment with high tolerability and no serious adverse effects. There was no significant difference between the treatment response based on age, gender, and disease duration, and this means that the treatment is effective regardless of the patient subgroup. Topical tranexamic acid is a potentially useful adjunct or substitution to conventional depigmenting treatment, due to its good safety profile and acceptable clinical results, which can be considered practical as part of a regular dermatological treatment. Longer follow-up randomized controlled trials should be considered to determine the long-term efficacy and recurrence.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Farhad Ali, Yamna Hassan
Drafting or Revising Critically:	Humaira Wazir, Kashmala
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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