# Assessment of the Efficacy of Tranexamic Acid Solution 5% in the Treatment of Melasma in Patients of South Asian Descent

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## PRATICE **POINTS**

- Tranexamic acid (TA) solution 5% is an efficacious treatment for skin of color patients with melasma.
- Topical TA is a treatment alternative for patients who may not be able to tolerate oral TA.
- Our study revealed the greatest efficacy for TA solution 5% was seen on the forehead and malar region, with less efficacy on the chin.

Melasma is a common dermatologic condition affecting all skin types. Increasing rates of melasma warrant identification of a reliable topical treatment. In recent years, off-label tranexamic acid (TA) has emerged as a potential treatment of melasma. Although the mechanism of action remains unclear, it is thought that TA inhibits melanin synthesis by blocking the interaction between melanocytes and keratinocytes while reversing the abnormal dermal changes associated with melasma. Our study assessed the efficacy of TA solution 5% for the treatment of melasma in patients with darker skin types.

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Melasma is a complex, long-lasting, acquired dermatologic pigmentation disorder resulting in grey-brown patches that last for more than 3 months. Sun-exposed areas including the nose, cheeks, forehead, and forearms are most likely to be affected.[1] In Southeast Asia, 0.25% to 4% of the population affected by melasma is aged 30 to 40 years.[2] In particular, melasma is a concern among pregnant women due to increased levels of melanocyte-stimulating hormones (MSHs) and is impacted by genetics, hormonal influence, and exposure to UV light.[3,4] In Pakistan, approximately 46% of women are affected by melasma during pregnancy.[2,5] Although few studies have focused on the clinical approaches to melasma in darker skin types, it continues to disproportionately affect the skin of color population.[4]

The areas of hyperpigmentation seen in melasma exhibit increased deposition of melanin in the epidermis and dermis, but melanocytes are not elevated. However, in areas of hyperpigmentation, the melanocytes are larger and more dendritic and demonstrate an increased level of melanogenesis.[6] During pregnancy, especially in the third trimester, elevated levels of estrogen, progesterone, and MSH often are found in association with melasma.[7] Tyrosinase (TYR) activity increases and cellular proliferation is reduced after treatment of melanocytes in culture with β-estradiol.[8] Sex steroids increase transcription of genes encoding melanogenic enzymes in normal human melanocytes, especially TYR.[9] These results are consistent with the notable increases in melanin synthesis and TYR activity reported for normal human melanocytes under similar conditions in culture.[10] Because melanocytes

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The authors report no conflict of interest.

The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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contain both cytosolic and nuclear estrogen receptors, melanocytes in patients with melasma may be inherently more sensitive to the stimulatory effects of estrogens and possibly other steroid hormones.[11]

The current treatment options for melasma have varying levels of success and include topical depigmenting agents such as hydroquinone, tretinoin, azelaic acid, kojic acid, and corticosteroids; dermabrasion; and chemical peels.[12-14] Chemical peels with glycolic acid, salicylic acid, lactic acid, trichloroacetic acid, and phenol, as well as laser therapy, are reliable management options.[13,14] Traditionally, melasma has been treated with a combination of modalities along with photoprotection and trigger avoidance.[12]

The efficacy and safety of the available therapies for melasma are still controversial and require further exploration. In recent years, off-label tranexamic acid (TA) has emerged as a potential therapy for melasma. Although the mechanism of action remains unclear, TA may inhibit melanin synthesis by blocking the interaction between melanocytes and keratinocytes.[15] Tranexamic acid also may reverse the abnormal dermal changes associated with melasma by inhibiting melanogenesis and angiogenesis.[16]

Although various therapeutic options exist for melasma, the search for a reliable option in patients with darker skin types continues.[13] We sought to evaluate the efficacy of TA solution 5% in reducing the severity of melasma in South Asian patients, thereby improving patient outcomes and maximizing patient satisfaction. Topical TA is inexpensive and readily accessible and does not cause systemic side effects. These qualities make it a promising treatment compared to traditional therapies.

## Methods

We conducted a randomized controlled trial at Rawalpindi Medical Institute (Punjab, Pakistan). The researchers obtained informed consent for all enrolled patients. Cases were sampled from the original patient population seen at the office using nonprobability consecutive sampling. The sample size was calculated with a 95% CI, margin of error of 9%, and expected percentage of efficacy of 86.1% by using TA solution 5%. South Asian male and female patients aged 20 to 45 years with melasma were included in the analysis. Patients were excluded if they were already taking TA, oral contraceptive pills, or photosensitizing drugs (eg, nonsteroidal anti-inflammatory drugs, tetracyclines, phenytoin, carbamazepine); were pregnant; had chronic kidney disease (creatinine >2.0 mg/dL); had cardiac abnormalities (abnormal electrocardiogram); had hematologic disorders (international normalized ratio >2); or had received another melasma treatment within the last 3 to 6 months.

All enrolled patients underwent a detailed history and physical examination. Patient demographics were subsequently noted, including age, sex, history of diabetes mellitus or hypertension, and duration of melasma. The melasma area and severity index (MASI) score of each patient was calculated at baseline, and a corresponding photograph was taken.

The topical solution was prepared with 5 g of TA dissolved in 10 cc of ethanol at 96 °F, 10 cc of 1,3-butanediol, and distilled water up to 100 cc. The TA solution was applied to the affected areas once daily by the patient for 12 weeks. Each application covered the affected areas completely. Patients were instructed to apply sunscreen with sun protection factor 60 to those same areas for UV protection after 15 minutes of TA application. Biweekly follow-ups were scheduled during the trial, and the MASI score was recorded at these visits. If the mean MASI score was reduced by half after 12 weeks of treatment, then the treatment was considered efficacious with a 95% CI.

The percentage reduction from baseline was calculated as follows: percentage reduction=(baseline score–follow-up score)/baseline score×100.

*Statistical Analysis*—Data were analyzed in SPSS Statistics 25 (IBM). The quantitative variables of age, duration of melasma, and body mass index were presented as mean (SD). Qualitative variables such as sex, history of diabetes mellitus or hypertension, site of melasma, and efficacy were presented as frequencies and percentages. Mean MASI scores at baseline and 12 weeks posttreatment were compared using a paired *t* test ($P \leq .05$). Data were stratified for age, sex, history of diabetes mellitus or hypertension, site of melasma, and duration of melasma, and a $\chi^2$ test was applied to compare efficacy in stratified groups ($P \leq .05$).

## Results

Sixty patients were enrolled in the study. Of them, 17 (28.33%) were male, and 43 (71.67%) were female (2:5 ratio). They ranged in age from 20 to 45 years (mean [SD], 31.93 [6.26] years). Thirty-seven patients (61.67%) were aged 31 to 45 years of age (Table 1). The mean (SD) duration of disease was 10.18 (2.10) months. The response to TA was recorded based on patient distribution according to the site of melasma as well as history of diabetes mellitus and hypertension.

Topical TA was found to be efficacious for melasma in 50 (83.33%) patients. The mean (SD) baseline and week 12 MASI scores were 23.15 (5.02) and 12.71 (4.10) ($P<.0001$), respectively (Table 2). The stratification of efficacy with respect to age, sex, duration of melasma, site of melasma, and history of diabetes mellitus or hypertension is shown in the eTable. The site of melasma was significant with respect to stratification of efficacy. On the forehead, TA was found to be efficacious in 11 patients and nonefficacious in 0 patients ($P=.036$). In the malar region, it was efficacious in 16 patients and nonefficacious in 1 patient ($P=.036$). Finally, on the chin, it was efficacious in 23 patients and nonefficacious in 9 patients ($P=.036$).



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**TABLE 1.** Demographics of Melasma Patients Treated With TA Solution 5% (N=50)

| Demographic | n (%) |
|---|---|
| Age group | |
| 20–30 y | 23 (38.33) |
| 31–45 y | 37 (61.67) |
| Sex | |
| Female | 43 (71.67) |
| Male | 17 (28.33) |
| Duration of melasma | |
| ≤12 mo | 49 (81.67) |
| >12 mo | 11 (18.33) |
| Site of melasma | |
| Forehead | 11 (18.33) |
| Malar region | 17 (28.33) |
| Chin | 32 (53.33) |
| History of DM | |
| DM | 16 (26.67) |
| No DM | 44 (73.33) |
| History of HTN | |
| HTN | 11 (18.33) |
| No HTN | 49 (81.67) |

Abbreviations: DM, diabetes mellitus; HTN, hypertension; TA, tranexamic acid.

**TABLE 2.** Efficacy of Melasma Treatment With TA Solution 5% (N=60)

| Assessment | Treatment response |
|---|---|
| Efficacy (>50% reduction in MASI score from baseline), n (%) | |
| Efficacious | 50 (83.33) |
| Not efficacious | 10 (16.67) |
| MASI score, mean (SD) | |
| Baseline | 23.15 (5.02) |
| Week 12 | 12.71 (4.10) |
| Change from baseline[a] | 10.44 (0.92) |

Abbreviations: MASI, melasma area and severity index; TA, tranexamic acid.

[a]$P<.0001$.

## Comment

*Melasma Presentation and Development*—Melasma is a chronic skin condition that more often affects patients with darker skin types. This condition is characterized by hyperpigmentation of skin that is directly exposed to the sun, such as the cheek, nose, forehead, and above the upper lip.[17] Although the mechanism behind how melasma develops is unknown, one theory suggests that UV light can lead to increased plasmin in keratinocytes.[18] This increased plasmin will thereby increase the arachidonic acid and α-MSH, leading to the observed uneven hyperpigmentation that is notable in melasma. Melasma is common in patients using oral contraceptives or expired cosmetic drugs; in those who are pregnant; and in those with liver dysfunction.[18] Melasma has a negative impact on patients' quality of life because of substantial psychological and social distress. Thus, finding an accessible treatment is imperative.[19]

*Melasma Management*—The most common treatments for melasma have been topical bleaching agents and photoprotection. Combination therapy options include chemical peels, dermabrasion, and laser treatments, though they present with limited efficacy.[17,20] Because melasma focuses on pigmentation correction, topical treatments work to disturb melanocyte pigment production at the enzymatic level.[21] Tyrosinase is rate limiting in melanin production, as it converts L-tyrosinase to L-3,4-dihydroxyphenylalanine, using copper to interact with L-3,4-dihydroxyphenylalanine as a cofactor in the active site.[22] Therefore, tyrosine is a major target for many drugs that have been developed for melasma to decrease melaninization.[21]

Recently, research has focused on the effects of topical, intradermal, and oral TA for melasma.[17] Tranexamic acid most commonly has been used in medicine as a fibrinolytic agent because of its antiplasmin properties. It has been hypothesized that TA can inhibit the release of paracrine melanogenic factors that normally act to stimulate melanocytes.[17] Although studies have supported the safety and efficacy of TA, there remains a lack of clinical studies that are sufficiently powered. No definitive consensus on the use of TA for melasma currently exists, which indicates the need for large-scale, randomized, controlled trials.[23]

One trial (N=25) found that TA solution 5% achieved efficacy (>50% reduction in MASI score from baseline) in 86.1% of patients with melasma.[24] In another study (N=18), topical TA 5% achieved efficacy (>50% reduction in MASI score) in 86% of patients with melasma.[25]

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*Melasma Comorbidities*—To determine if certain comorbidities, such as diabetes mellitus or hypertension, influenced the progression of melasma, we stratified the efficacy results for patients with these 2 comorbidities, which showed no significant difference ($P=.794$ and $P=.101$, respectively). Thus, the relatively higher prevalence of diabetes mellitus (16 patients) and hypertension (11 patients) did not contribute to the efficacy of TA in lowering MASI scores over the 12-week period, which supports the findings of Doolan and Gupta,[26] who investigated the endocrinologic conditions associated with melasma and found no such association with diabetes mellitus or hypertension.

*TA Formulations for Melasma*—The efficacy of topical TA has been explored in several studies. Six studies with sample sizes of 13 to 50 patients each showed statistically significant differences in MASI scores between baseline and following TA treatment ($P<.001$).[27-32] Several formulations and regimens were utilized, including TA cream 3% for 12 weeks, TA gel 5% for 12 weeks, TA solution 3% for 12 weeks, TA liposome 5% for 12 weeks, and TA solution 2% for 12 weeks.[18] Additionally, these studies found TA to be effective in limiting dyschromia and decreasing MASI scores. There were no statistically significant differences between formulations and method of application. Topical TA has been found to be just as effective as other treatments for melasma, including intradermal TA injections, topical hydroquinone, and a combination of topical hydroquinone and dexamethasone.[18]

Further study of the efficacy of intradermal TA is necessary because many human trials have lacked statistical significance or a control group. Lee et al[32] conducted a trial of 100 female patients who received weekly intradermal TA microinjections for 12 weeks. After 8 and 12 weeks, MASI scores decreased significantly ($P<.01$).[32] Similarly, Badran et al[33] observed 60 female patients in 3 trial groups: group A received TA (4 mg/mL) intradermal injections every 2 weeks, group B received TA (10 mg/mL) intradermal injections every 2 weeks, and group C received TA cream 10% twice daily. Although all groups showed improvement in MASI, group B, which had the highest intradermal TA concentration, exhibited the most improvement. Thus, it was determined that intradermal application led to better results, but the cream was still effective.[33]

Saki et al[34] conducted a randomized, split-face trial of 37 patients comparing the efficacy of intradermal TA and topical hydroquinone. Each group was treated with either monthly intradermal TA injections or nightly hydroquinone for 3 months. After 4 weeks of treatment, TA initially had a greater improvement. However, after 20 weeks, the overall changes were not significant between the 2 groups.[34] Pazyar et al[35] conducted a randomized, split-face trial of 49 patients comparing the efficacy of intradermal TA and hydroquinone cream. After 24 weeks of biweekly TA injections or twice-daily hydroquinone, there were no statistically significant differences in the decreased MASI scores between treatments.[35] Additional large, double-blind, controlled trials are needed to thoroughly assess the role of intradermal TA in comparison to its treatment counterpart of hydroquinone.

Ebrahimi and Naeini[29] conducted a 12-week, double-blind, split-phase trial of 50 Iranian melasma patients, which showed that 27.3% of patients rated the improvement in melasma as excellent, 42.4% as good, and 30.3% as fair after using TA solution 3%. Wu et al[36] also showed a total melasma improvement rate of 80.9% in 256 patients with long-term oral use of TA. In a study by Kim et al[31] (N=245), the mean MASI score considerably decreased after topical TA use, with a total response rate of 95.6%. In another study, Atefi et al[37] presented significantly increased levels of satisfaction in patients treated with topical TA 5% vs hydroquinone ($P=.015$).

*Melasma in Patients With Darker Skin Types*—Special attention must be given to choosing the appropriate medication in melasma patients with darker skin types, as there is an increased risk for postinflammatory hyperpigmentation. Currently, few randomized controlled trials exist that fulfill the criteria of evaluating pharmacologic options for patients with melasma, and even fewer studies solely focus on patients with darker skin types.[38] In addition to treatment advances, patients must be educated on the need to avoid sun exposure when possible or to use photoprotection, especially in the South Asian region, where these practices rarely are taught. Our study provided a unique analysis regarding the efficacy of TA solution 5% for the treatment of melasma in patients of South Asian descent. Clinicians can use these findings as a foundation for treating all patients with melasma but particularly those with darker skin types.

*Study Limitations*—Our study consisted of 60 patients; although our study had more patients than similar trials, larger studies are needed. Additionally, other variables were excluded from our analysis, such as comorbidities beyond diabetes mellitus and hypertension.

## Conclusion

This study contributes to the growing field of melasma therapeutics by evaluating the efficacy of using TA solution 5% for the treatment of melasma in South Asian patients with darker skin types. Clinicians may use our study to broaden their treatment options for a common condition while also addressing the lack of clinical options for patients with darker skin types. Further studies investigating the effectiveness of TA in large clinical trials in humans are warranted to understand the efficacy and the risk for any complications.

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## APPENDIX

**eTABLE. Stratification of Efficacy of Melasma Treatment With TA Solution 5% (N=60)**

| Demographic | No. of patients | *P* value |
|---|---|---|
| **Age group** | | |
| 20–30 y | | |
| Efficacious | 21 | .191 |
| Not efficacious | 2 | .191 |
| 31–45 y | | |
| Efficacious | 29 | .191 |
| Not efficacious | 8 | .191 |
| **Sex** | | |
| Female | | |
| Efficacious | 36 | .898 |
| Not efficacious | 7 | .898 |
| Male | | |
| Efficacious | 14 | .898 |
| Not efficacious | 3 | .898 |
| **Duration of melasma** | | |
| ≤12 mo | | |
| Efficacious | 41 | .881 |
| Not efficacious | 8 | .881 |
| >12 mo | | |
| Efficacious | 9 | .881 |
| Not efficacious | 2 | .881 |
| **Site of melasma** | | |
| Forehead | | |
| Efficacious | 11 | .036 |
| Not efficacious | 0 | .036 |
| **Site of melasma** (continued) | | |
| Malar region | | |
| Efficacious | 16 | .036 |
| Not efficacious | 1 | .036 |
| Chin | | |
| Efficacious | 23 | .036 |
| Not efficacious | 9 | .036 |
| **History of DM** | | |
| DM | | |
| Efficacious | 13 | .794 |
| Not efficacious | 3 | .794 |
| No DM | | |
| Efficacious | 37 | .794 |
| Not efficacious | 7 | .794 |
| **History of HTN** | | |
| HTN | | |
| Efficacious | 11 | .101 |
| Not efficacious | 0 | .101 |
| No HTN | | |
| Efficacious | 39 | .101 |
| Not efficacious | 10 | .101 |

Abbreviations: DM, diabetes mellitus; HTN, hypertension; TA, tranexamic acid.

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