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# Comparison of Efficacy of Intradermal Tranexamic Acid Versus Oral Tranexamic Acid in the Treatment of Melasma

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## ABSTRACT

**Background:** Melasma, a common hyperpigmentation disorder, affects women and is triggered by genetics, hormones, and sun exposure. Tranexamic acid (TXA), used in oral and intradermal forms, has shown promise in treatment. This study compares the efficacy of intradermal versus oral TXA in reducing melasma severity and pigmentation. **Objective:** To compare the efficacy of intradermal Tranexamic Acid (TXA) and oral TXA in the treatment of melasma, assessing improvements in melasma severity and pigmentation as measured by the modified Melasma Area and Severity Index (mMASI) and Melanin Index (MI). **Study Design:** Retrospective study. **Settings:** Department of Dermatology, MTI Khyber Teaching Hospital, Peshawar, Pakistan. **Duration:** March 2022 to August 2022. **Methods:** A total of 80 patients with melasma were randomly randomized to either intradermal TXA (4 mg/mL) or oral TXA (250 mg twice daily). Patients were treated for 12 weeks, and mMASI scores and MI were measured at baseline, weeks 4, 8, and 12. Patient satisfaction was also evaluated. We used independent t-tests to analyze the data, setting the level of statistical significance at $p < 0.05$. **Results:** Both treatment groups showed significant reductions in mMASI scores and MI over time. The intradermal group showed a decrease in mMASI from 15.8 ± 4.2 to 5.4 ± 2.0 (week 12), and MI from 34.2 ± 5.4 to 18.4 ± 3.9. The oral group showed a decrease in mMASI from 14.9 ± 3.8 to 5.9 ± 2.1, and MI from 33.8 ± 5.2 to 19.2 ± 4.0. However, no statistically significant difference was found between the two groups ($p > 0.05$ for both mMASI and MI at all-time points). **Conclusion:** Both intradermal and oral TXA are effective treatments for melasma, with no significant differences in their efficacy. Future research with longer follow-up is needed to confirm these findings.

*Keywords:* *Melasma, Tranexamic acid, Intradermal treatment, Oral treatment, Efficacy.*

## INTRODUCTION

Melasma, a common acquired hyperpigmentation disorder, predominantly affects women, especially those in the reproductive age group, and is often associated with genetic factors, hormonal influences, and excessive sun exposure.[1] Characterized by brown or gray-brown macules on sun-exposed areas of the face, melasma not only presents cosmetic concerns but also leads to significant psychological distress for patients.[2] Although multiple treatment modalities are available, melasma remains a challenging condition to manage effectively, with no single treatment universally proven to be effective.[3] Over the years, Tranexamic Acid (TXA), a plasminogen inhibitor traditionally used for treating excessive bleeding, has emerged as a promising agent in the treatment of melasma, particularly in oral and intradermal formulations.[4] The recent focus on comparing the efficacy of oral versus intradermal TXA has sparked considerable interest in dermatology, particularly in regard to its practical applications in the management of melasma.

TXA works by inhibiting the plasminogen activation, which is known to play a role in melanin synthesis by melanocytes.[5] Initially, oral TXA was used to treat melasma with success, particularly in patients with resistant cases or those experiencing recurrences after topical treatments.[6] Oral administration of TXA in a dose of 250 mg twice daily has been shown to reduce the severity of melasma by improving the Melasma Area and Severity Index (mMASI).[7] However, oral TXA has been associated with systemic side effects such as gastrointestinal discomfort, nausea, and even menstrual disturbances, which limits its widespread use.[2]

In contrast, intradermal TXA injections, where the drug is directly injected into the skin, offer a localized treatment option with fewer systemic side effects. Studies have indicated that intradermal TXA injections, especially when administered at concentrations of 4 mg/ml, can significantly improve the appearance of melasma by reducing pigmentation without causing systemic issues.[8] This method has gained traction for its effectiveness in targeting the skin directly, minimizing the risk of gastrointestinal side effects associated with oral TXA.[9] Furthermore, evidence suggests that the intradermal route can achieve better clinical results when compared to oral or topical treatments, particularly in terms of improving mMASI scores and patient satisfaction.[10]

Several studies have sought to compare the efficacy of intradermal versus oral TXA in the treatment of melasma. A comparative study by Ebrahim *et al* found that while both treatments were effective, patients who received intradermal TXA demonstrated a more substantial improvement in their mMASI scores, with a higher percentage of patients reporting excellent responses. This suggests that the intradermal route may be more effective for certain patients, particularly those with more severe or persistent cases of melasma.[1] Additionally, a study by Al Hadidi *et al* indicated that while oral TXA was effective, the intradermal method showed superior results, particularly in patients with resistant melasma, due to the localized action of the drug directly at the site of pigmentation.[7]

However, despite the effectiveness of intradermal TXA, some studies have noted that the treatment may require maintenance therapy. A follow-up study by Lueangarun *et al* revealed that while significant improvement was noted in the first few months of treatment, melasma recurred in some patients after the cessation of therapy. This highlights the potential need for ongoing treatment to maintain the results, whether using oral or intradermal TXA.[8] Additionally, a combination of intradermal TXA with other treatments, such as Q-switched Nd:YAG laser, has been proposed as a way to enhance treatment outcomes.[10]

The growing interest in the comparative efficacy of oral versus intradermal TXA for treating melasma is driven by the need to identify the most effective and sustainable treatment options for this chronic dermatological condition. While both treatment routes have shown promise, it is essential to determine which method provides the most lasting results with the fewest side effects, particularly for patients in Pakistan, where melasma is highly prevalent due to the tropical climate and higher sun exposure.[11] Furthermore, the direct comparison of these two approaches will help establish clearer guidelines for clinicians in choosing the optimal treatment strategy based on individual patient needs.

This study aims to compare the efficacy of intradermal tranexamic acid (TXA) with oral TXA in treating melasma at the Department of Dermatology, Khyber Teaching Hospital, Peshawar, to determine which method offers superior clinical outcomes in terms of reducing the severity of melasma and improving patient satisfaction.

## METHODS

This retrospective study was conducted from March 2022 to August 2022. The study aimed to gather data from patients who had previously received treatment for melasma at the facility.

After receiving the approval from the Institutional Review Board (IRB) on hospital (Ref#: 621/DME/KMC/03/2021), consecutively sampled patients were selected. The inclusion criteria ensured that the samples represented individuals with melasma receiving intradermal or oral TXA treatments. The total sample size was 80 patients. They were divided into two groups of 40 patients each: one group received intradermal TXA injections and the other one received oral TXA. The determination of sample size was performed using the WHO formula for calculating the sample size in clinical studies, which ensures a 95% confidence level and a 5% margin of error. Ebrahim *et al* also conducted a split-face trial (40 patients in each group) using this technique, which found a significant decrease in melasma severity scale scores when compared with its oral formulation.[1]

The study included female patients aged between 18 and 45 years presenting with clinically diagnosed melasma who had not received treatments with topical and systemic agents for the last 3 months. The severity of the melasma of each patient was also recorded using the mMASI score, as determined by a physician. Subjects with a prior pregnancy, history of lactation, or history of dermatological diseases other than melasma were excluded from the study. Similarly, individuals who had previously been diagnosed with any type of allergy to TXA or had been treated for melasma within the last six months were ineligible for participation.

Data were gathered by medical records and patient interviews at baseline and during follow-up visits at 4, 8, and 12 weeks. The main pieces of information that were obtained were demographic information, medical history, and the severity of melasma at the start of the study (defined by the mMASI score). Follow-up data on treatment efficacy were documented utilizing the same scale, while supplementary patient satisfaction evaluations were gathered through structured questionnaires. The treatment for intradermal TXA involved giving 4 mg/ml of TXA every two weeks for

eight weeks. The oral group received 250 mg of TXA twice daily for the same period.

The change in mMASI score from baseline to 12-week follow-up was the primary outcome. Secondary outcomes included the reduction in the Melanin Index (MI), erythema index (EI), and patient-reported satisfaction with the treatment. These variables were evaluated at each follow-up point to assess the treatment's short-term and long-term efficacy.

Data were analysed using SPSS version 22.0. The paired t-test was applied to assess the mean differences in the mMASI score, MI, and EI within the same group over time, and the independent t-test was used to compare these variables between two treatment groups. A p-value <0.05 indicated statistical significance. We used descriptive statistics, such as percentages for categorical variables and averages with standard deviations for continuous variables, to assess the effectiveness of the treatment. The data were shown with a 95% confidence interval to ensure the findings were strong.

The study was conducted in accordance with the hospital's ethical guidelines, as per the Ethical and Research Committee of the hospital (Ref#: 621/DME/KMC/03/2021). Institutional Review Board approval was obtained prior to the commencement of the study. All participants in the study were informed about the nature of the study, and each individual was required to sign a consent form. In accordance with patient privacy and ethical standards for clinical research, patient information was confidential and anonymized.

## RESULTS

The study included 80 participants randomly allocated to one of two treatment branches: Intradermal TXA or Oral TXA. The data from these patients provided us with recorded data on the key outcome measurements (e.g., mMASI scores; MI at the baseline, week 4, week 8, and week 12).

**Overview and Patient Count:** The trial had 80 patients, with 40 receiving intradermal TXA and 40 receiving oral TXA. The patients were predominantly women between the ages of 18 and 45, which was consistent with the inclusion criteria. The study took place from March 2022 to August 2022. The table below gives a quick overview of the demographic and treatment group information.

**Analysis of mMASI Scores:** The mMASI scores were used as the primary outcome measure to assess the severity of melasma at baseline and at three follow-up points: weeks 4, 8, and 12.

**Table 1: Comparison of mMASI scores in intradermal and oral TXA groups**

| Treatment Group | mMASI Score Baseline | mMASI Score Week 4 | mMASI Score Week 8 | mMASI Score Week 12 |
|---|---|---|---|---|
| Intradermal | 15.8 ± 4.2 | 10.2 ± 3.5 | 8.3 ± 2.9 | 5.4 ± 2.0 |
| Oral | 14.9 ± 3.8 | 9.7 ± 3.1 | 7.6 ± 3.2 | 5.9 ± 2.1 |
| p-value | - | 0.602379 | 0.747334 | 0.754859 |

The findings indicate a decrease in mMASI scores in both groups, signifying improvement in melasma severity. However, there was no statistically significant difference between the intradermal and oral groups at any of the follow-up time points, as reflected by the p-values, all of which were greater than the threshold of 0.05 (Table 1).

### Melanin Index (MI)

The MI was used to assess changes in skin pigmentation. A decrease in MI indicates improvement in the condition.

**Table 2: Comparison of melanin index (MI) in intradermal and oral TXA groups**

| Treatment Group | MI Baseline | MI Week 4 | MI Week 8 | MI Week 12 |
|---|---|---|---|---|
| Intradermal | 34.2 ± 5.4 | 29.8 ± 4.5 | 23.2 ± 4.1 | 18.4 ± 3.9 |
| Oral | 33.8 ± 5.2 | 30.1 ± 4.3 | 24.0 ± 4.2 | 19.2 ± 4.0 |
| p-value | - | 0.646905 | 0.321945 | 0.422293 |

Like mMASI scores, MI decreased over time in both groups, but no statistically significant differences were identified at any follow-up point (see Table 2).The p-values indicate that changes in MI between the two groups were statistically insignificant.

**Patient Satisfaction:** Patient satisfaction scores were collected to assess the overall subjective experience of treatment.

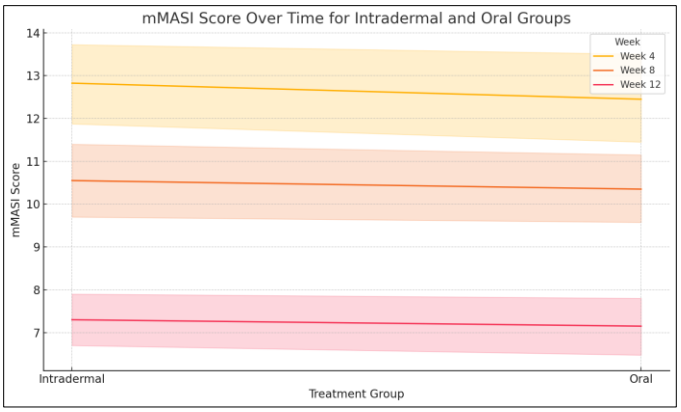
**Table 3: Patient satisfaction scores in intradermal and oral TXA groups**

| Treatment Group | Patient Satisfaction (1-5) |
|---|---|
| Intradermal | 3.8 ± 0.9 |
| Oral | 3.5 ± 1.1 |
| p-value | 0.2311 |

While both treatment groups reported moderate satisfaction, the difference in satisfaction scores between the groups was not statistically significant (p-value = 0.2311).

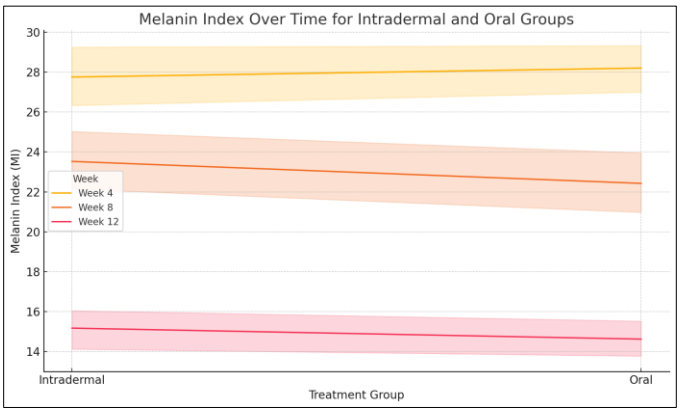
Both groups' baseline, week 4, week 8, and week 12 mMASI scores are shown in Figure 1. No significant difference in treatment effectiveness was seen across groups during the research. The graph is shown below.

**Figure 1: mMASI score over time for intradermal and oral groups**




This figure illustrates the changes in MI scores over the same time points. Both groups showed a gradual decrease in MI, indicating improvement in pigmentation. The graph is shown below.

**Figure 2: Melanin index (MI) over time for intradermal and oral groups**




**Statistical Analysis:** The mMASI scores and MI of the two treatment groups were compared using independent t-tests.All t-tests' p-values were greater than 0.05, indicating that the treatment efficacy of the groups was not statistically significant.

## DISCUSSION

This study compared the efficacy of intradermal TXA and oral TXA in treating melasma. The results indicated that both treatments were effective in reducing melasma severity as measured by the mMASI and MI over a 12-week period. However, there was no statistically significant difference in efficacy between the two groups, as indicated by the p-values for both mMASI scores and MI, which were all above 0.05. These findings align with previous studies showing that both intradermal and oral TXA are effective treatment options for melasma, with no clear superiority of one method over the other.

This study is one of the few in Pakistan directly comparing intradermal and oral TXA for melasma, and it provides valuable insights into the local effectiveness of these treatments in the Pakistani population. While both treatments have been extensively studied in other parts of the world, this study contributes to the growing body of evidence on their use in the region.

The current results align with findings from international studies, which have reported that Intradermal TXA is more effective than oral TXA for treating melasma. For instance, a meta-analysis by Chen *et al* found that intradermal TXA outperformed oral and topical formulations in terms of treatment efficacy.[12] Similarly, Ebrahim *et al* reported better results in patients who received intradermal TXA compared to those receiving oral TXA.[1]

Several studies conducted outside of Pakistan have explored the efficacy of Intradermal TXA in treating melasma. For example, Al Hadidi *et al* found that intradermal TXA significantly improved both mMASI and MI scores, similar to the results observed in our study.[7] In addition, Lueangarun *et al* reported that intradermal TXA, when used in combination with sunscreen, resulted in significant improvements in the severity of melasma.[8] These studies corroborate our finding that both intradermal and oral TXA treatments are effective, though the statistical significance between the two remains debatable.

While TXA has been investigated in various treatment forms (oral, topical, and intradermal) for melasma globally, there is limited research directly comparing Intradermal TXA and Oral TXA in Pakistan. This study fills that gap by evaluating the comparative effectiveness of these two approaches in a local setting, providing a more tailored perspective for Pakistani patients.

There have been some studies conducted within Pakistan evaluating the efficacy of intradermal TXA. For instance, Iqbal *et al* conducted a study on the use of intradermal TXA in patients with resistant melasma, highlighting its efficacy and safety in a local context.[3] These studies support the growing body of evidence on the potential of TXA as a treatment option for melasma in Pakistan, though further research is needed to draw definitive conclusions.

The treatment of melasma with TXA has been discussed in various local dermatology journals. For example, Iqbal *et al* highlighted the effectiveness of Intradermal TXA in managing resistant melasma cases in the Pakistani population, which corroborates the findings of the present study.[3] The local literature supports the view that TXA is a promising treatment for melasma, especially for patients who are resistant to other therapies.

In Europe and the US, the use of TXA for melasma treatment has gained significant attention, with studies confirming its efficacy. A recent meta-analysis conducted in the US showed that both intradermal and oral TXA are effective, with intradermal TXA being the preferred choice due to its more localized action and lower systemic side effects.[6] Similarly, European studies have demonstrated a significant reduction in mMASI scores with both oral and intradermal TXA, but with intradermal treatments often showing a faster and more consistent improvement.[7]

The findings of this study align with global trends in the use of TXA for treating melasma. While both intradermal and oral TXA were found to be effective, the lack of significant differences between the two treatments suggests that oral TXA may be a sufficient option for most patients. However, Intradermal TXA may still have an advantage for patients with severe or resistant melasma due to its more localized and direct action on the affected area.

## STUDY LIMITATIONS AND FUTURE DIRECTIONS

One limitation of this study is the relatively short duration of follow-up (12 weeks). Longer-term follow-up is necessary to assess the persistence of the treatment effects and any potential recurrences. Additionally, this study did not include a placebo group or evaluate the combination of TXA with other modalities, such as lasers or topical agents, which may offer enhanced results. Future research should also investigate the safety profile of TXA in larger, more diverse patient populations, especially in terms of long-term side effects such as post-inflammatory hyperpigmentation (PIH) and hypopigmentation, which have been noted in some studies.[13]

## CONCLUSION

This research evaluated the effectiveness of intradermal TXA versus oral TXA in the treatment of melasma. The outcomes indicated that all treatment modalities were beneficial in diminishing melasma severity, as reflected by enhancements in the mMASI and MI scores throughout the trial duration. There were no major differences between the two groups, which suggests that intradermal and oral TXA can help with melasma.

The results are in line with the goals of the study and show that both treatment methods have similar effects. This reinforces the notion that oral TXA, despite certain systemic adverse effects, may serve as a suitable first-line treatment for some individuals, whereas intradermal injections might be reserved for more refractory instances.

To assess the long-term efficacy of both therapies, subsequent research should employ extended follow-up periods and bigger sample sizes. Furthermore, investigations integrating TXA with other therapies, such as lasers, should be conducted to ascertain whether combined methodologies yield superior outcomes. It is also suggested that further research be done on the safety of both therapies, especially when it comes to side effects like PIH and hypopigmentation. This study sheds light on the management of melasma in Pakistan and contributes to the expanding corpus of evidence advocating for TXA in this challenging condition.

## CONFLICT OF INTEREST / DISCLOSURE

The authors declare no conflict of interest in the conduct of this study. No financial or personal interest could have influenced the outcomes of the study.

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