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Comparative Evaluation of Therapeutic Efficacy of Oral Tranexamic Acid versus its Intradermal Administration in Melasma – A Quasi-Experimental Study

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ABSTRACT

Objective: To compare the therapeutic efficacy of oral tranexamic acid versus transdermal tranexamic acid administration in patients with melasma.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan, May to Oct 2024.
Methodology: The study enrolled 104 patients with diagnosed melasma, who were divided in a 1:1 ratio into two groups, Group A and Group B. Informed consent was taken from all patients. Group A received intralesional tranexamic acid while Group B took oral tranexamic acid 250mg twice a day. Modified Melasma Area and Severity Index (mMASI) was calculated for each patient at baseline and monitoring of both groups was done on a monthly basis with mMASI for 3 months.
Results: The median age of this sample was 35.22±9.83 years, comprising 95(91.30%) females and 9(8.70%) males. Median baseline mMASI for Group A was 18.6(5.85) and for Group B, it was also 18.6(5.85). Comparison from baseline mMASI score showed a consistent reduction in mMASI scores at each follow-up (p=0.00). In our study population, 49(94.23%) patients in the intralesional group responded to treatment, whereas 47(90.38%) patients responded to treatment in the oral tranexamic acid group (p=0.72).
Conclusion: Both routes of tranexamic acid administration demonstrated high response rates with np statistically significant differences.

Keywords: Hyperpigmentation, Intradermal Injection, Melasma, Skin Pigmentation, Tranexamic Acid.

How to Cite This Article: *Malik A, Shahid MF, Ahmad MK, Khadam N, Manzoor T. Comparative Evaluation of Therapeutic Efficacy of Oral Tranexamic Acid versus its Intradermal Administration in Melasma – A Quasi-Experimental Study. Pak Armed Forces Med J 2025; 76(Suppl-2): S468-S472. DOI: https://doi.org/10.51253/pafmj.v76iSUPPL-2.12881*

INTRODUCTION

Melasma, a chronic hyperpigmentation disorder of the skin, affects more than 50% of the worldwide population.[1] It predominantly occurs in females and is more common in individuals with Fitzpatrick skin types II–V.[2,3] Major causative factors include sun exposure, oral contraceptives, family history and pregnancy.[4] Pathogenesis of melasma is, however, unclear and mainstay of treatment strategies is the inhibition of tyrosinase, which is involved in melanin synthesis in melanocytes.[5] Melasma is a benign condition and does not transform into melanoma or any other skin malignancy.[6] However, it has a significant effect on quality of life and leads to depression in the sufferers.[7] The severity of the condition can be represented using the modified Melasma Area and Severity Index (mMASI), which employs area of involvement and darkness of the skin to assess the severity of melasma, ranging from 0 to 24, with 24 being the most severe.[8] Higher scores have been linked to higher incidence of depression amongst melasma patients.[7] Treating melasma often presents a challenge. Current treatment strategies mainly employ the use of depigmenting agents, chemical peels and lasers as primaries, with tranexamic acid, oral or intradermal, glutathione oral or topical as adjuncts.[9] Both oral and intradermal forms of tranexamic acid have shown promise, but there is insufficient direct comparative data.[10] No comprehensive studies in Pakistan have specifically focused on comparing the efficacy of different routes of tranexamic acid administration for melasma. This study aims to provide valuable regional data, particularly for Fitzpatrick skin types III and IV, to improve treatment strategies for melasma in Pakistani clinical practice.

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Received: 10 Nov 2024; revision received: 12 Feb 2025; accepted: 20 Feb 2025

METHODOLOGY

This was a quasi-experimental study conducted at Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan, over a period of 6 months from

May to October 2024, after obtaining approval from the hospital Ethics Review Board (vide reference no. A/28/ER/520/23). A thorough informed, written consent was taken from the patients in Outpatient department (OPD) of Dermatology. Sample size was calculated by using Open Epi online Sample Size Calculator for Randomized Clinical trials / Cohort Studies, keeping the power of the study at 90% and a 5% margin of error with odds ratio (OR=19.592) for improvement in melasma by oral tranexamic acid as compared to intralesional route from a randomized open label trial.[11] Sample size came out to be 46, however for further accuracy, 104 patients were included. Patients were enrolled in a 1:1 ratio in Groups A and B. Group A received intralesional tranexamic acid while Group B took oral tranexamic acid.

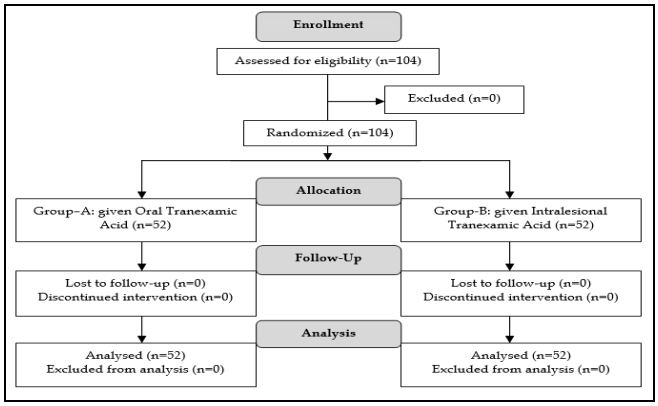

Figure: Patient Flow Diagram (n=104)

Inclusion Criteria: All patients, aged 20 to 60 years, belonging to either gender, diagnosed with melasma, in the OPD of Department of Dermatology were included in the study.

Exclusion Criteria: Patients having documented hypersensitivity to tranexamic acid or suffering from a chronic comorbid condition, using photosensitizing drugs, topical depigmenting agents or those who had received any treatment for melasma in the last 2 months were excluded from the study. Patients were subjected to Wood Lamp's examination in the OPD and type of melasma was diagnosed. Modified MASI was calculated for each patient at baseline. The score was calculated by using the Area (A, as percentage involvement of the facial region) and Darkness (D, ranging from 0 = Absent to 4 = severe) of melasma at different facial locations (forehead, left/right malar, chin) by the following formula: 0.3A (f) x D(f) + 0.3A(Lm) x D(Lm) + 0.3A(Rm) x D(Rm) + 0.1A(c) x D(c). Patients were then prescribed either oral tranexamic acid 250mg twice a day or intralesional tranexamic acid, with Injection TransamineR 500mg/5ml injected directly into the lesion using insulin syringe of 100 units. The affected area was cleaned prior to intralesional injection thoroughly so as to remove any cosmetic or sunblock preparation. Topical numbing agent NumCainR (7% Tetracaine + 7% Lidocaine) cream was applied to the area 45 minutes prior to the injection. The affected area was then injected repeatedly, 1 cm apart, at an angle of 15 degrees up to dermis, with 0.1ml aliquots so as to form a wheal at every site. This corresponded to 10 units on the insulin syringe and contained 10mg of tranexamic acid in every injection. The injected sites were cleaned again 30 minutes after the procedure using alcohol pad and ice compresses were done. This was repeated every 2 weeks. Patients were also advised to observe protection from sunlight using both physical and topical methods. Monitoring of the patients of both groups was done on a monthly basis and mMASI was calculated. This was done for 3 months and data was included in the final analysis. Data was entered in Statistical Package for Social Sciences (SPSS) software version 25.00 and analyzed. Normality of the mMASI scores was checked using Kolmogorov-Smirnov test. Medians and interquartile ranges were calculated for the mMASI scores. For comparison of ranks of data at different temporal junctures, Friedman test was used with Post-Hoc analysis using Wilcoxon signed-rank test for pinpointing where differences occur in time. For comparison between the oral and intralesional groups, Mann-Whitney U test was applied where a *p*-value of <0.05 was considered as significant.

RESULTS

This study included 104 patients, out of which 95(91.30%) were females and 9(8.70%) males, with mean age being 35.22±9.83 years. The study population was divided into Groups A and B, each having 52 patients. Demographic characteristics of both groups have been summarized in Table-I.

Median baseline mMASI was 18.60 (IQR) for the study population with median for Group A being IQR: 18.60 (), and the same for Group B. The mMASI scores were compared separately for both groups which showed that the melasma scores improved post intervention in both groups, indicated by a *p*-value of <0.00. Intragroup comparison of baseline mMASI score was compared with 1st, 2nd and 3rd month mMASI scores to see where the change occurs. In both

treatment groups, a consistent reduction in mMASI scores at each follow-up was seen (p=0.00) as shown in Table-II.

Table-I: Comparison of Basic Characteristics of Both Groups (n=104)

Characteristic		Group A (n=52) n(%)	Group B (n=52) n(%)	p-value
Age (years) (Mean±SD)		34.13±11.37	36.3±11.37	0.26
Gender	Male	7 (13.50%)	2 (3.80%)	0.16
	Female	45 (86.50%)	50 (96.20%)	
Type of Melasma	Epidermal	21 (40.40%)	17 (32.70%)	0.37
	Dermal	9 (17.30%)	6 (11.50%)	
	Mixed	22 (42.30%)	29 (55.80%)	
Location of Melasma	Centrofacial	12 (23.10%)	12 (23.10%)	1.00
	Malar	15 (28.80%)	15 (28.80%)	
	Forehead	13 (25.00%)	13 (25.00%)	
	Chin	6 (11.50%)	6 (11.50%)	
	Diffuse	6 (11.50%)	6 (11.50%)	

Table-II: Comparison Between Baseline and Follow up (n=104)

Comparison	Group	Baseline Median (IQR)	Follow up Median (IQR)	p-value
1 month-Baseline	Intralesional (n=52)	18.60(5.85)	18.00(6.00)	0.00
	Oral (n=52)	18.60(5.85)	18.00(6.00)	0.00
2 months - Baseline	Intralesional (n=52)	18.60(5.85)	12.00(6.52)	<0.00
	Oral (n=52)	18.60(5.85)	11.25(4.72)	<0.00
3 months - Baseline	Intralesional (n=52)	18.60(5.85)	6.60(5.40)	<0.00
	Oral (n=52)	18.60(5.85)	6.15(3.22)	<0.00

At baseline, both groups had identical ranks and the test showed no significant difference between the groups (p=1.00) but at 3 months, Group B had a slightly higher mean rank, but the difference was not statistically significant (p=0.52).

Table-III: Comparison of mMASI between Oral and Intralesional at the end of trial period (n=104)

Time Point	Group	Median (IQR)	p-value
Baseline mMASI Score	Oral (n=52)	18.60(5.85)	1.00
	Intralesional (n=52)	18.60(5.85)	
3-month mMASI Score	Oral (n=52)	6.60(3.22)	0.52
	Intralesional (n=52)	6.15(5.40)	

Table-IV: Percentage Response Seen in Both Groups (n=104)

% Response	Oral Tranexamic Acid (n=52)	Intralesional Tranexamic Acid (n=52)	p-value
0 - 10%	4(7.69%)	3(5.76%)	0.46
10 - 25%	0(0.00%)	3(5.76%)	
25 - 50%	13(25.00%)	11(21.15%)	
50 - 75%	26(50.00%)	28(53.84%)	
75 - 100%	9(17.30%)	7(13.46%)	

The response of patients towards either treatment was also not found to differ significantly (p=0.49). Both groups had comparable responses in terms of percentage of resolution of melasma where more than 50% resolution of melasma was seen in 35(67.30%) cases in either group, as shown in Table-IV.

DISCUSSION

Both groups showed significant improvement in melasma scores from baseline to follow-up (p<0.00 in the Friedman test) and this improvement was observed across all temporal junctures, with a marked increase in negative ranks and a decrease in positive ranks in both groups (p=0.00), however, no significant difference was found between the groups in terms of the reduction in melasma scores, with a p-value of 1.00 at baseline and 0.52 at 3 months. Both treatments had similar response rates, with 94.23% of patients in Group A and 90.38% in Group B showing a positive response, but this difference was not statistically significant (p=0.72 and p=0.49, respectively). Histopathological evidence for effect of tranexamic acid on skin pigmentation in melasma exists, but with regards to route of administration, data are conflicting.[12] Findings of our study are in agreement with existing literature, where it was noted that the efficacy of the drug is not dependent on its route of administration.[13] In another study, similar results were reported.[14] Nevertheless, another study reported that intradermal route is superior for resistant melisma.[15] However, in a meta-analysis of 29 studies, tranexamic acid used as an adjunct besides routine topical agents was effective.[16] In another systematic review and meta-analysis, over 3000 patients were included and, not only were different routes of tranexamic acid administration compared, it was found that oral tranexamic acid was better in terms of its curative effect, where a combination of oral tranexamic acid and routine topical agents had the best effect.[17] Although oral route is associated with some gastrointestinal disturbances, it is superior to intralesional tranexamic acid.[18] On the other hand, some researchers reported that the intralesional administration was better than oral route.[19] One study compared different concentrations of tranexamic acid with each other and found that there was no significant difference between them, as they applied 4% hydroquinone (HQ) cream to one side of the face in both groups and reported that, although no significant difference existed at 4th week follow up, but at 8th and 12th week follow up, MASI score was significantly reduced in the 4% HQ group.[20] Other treatments that have been compared with tranexamic acid include platelet rich plasma (PRP) and

Magnesium Ascorbyl Phosphate (MAP) but found no significant difference between the two in a small scale trial was noted,[21] however, PRP has been reported as superior to intralesional tranexamic acid[22,23] and topical MAP with intralesional tranexamic acid was also reported to be effective.[24]

LIMITATIONS OF STUDY

Our study was limited by its small sample size, single-center design, and the absence of documentation of side effects due to time and resource constraints. Additionally, observer bias may have affected the accuracy of measurements, as the assessment of skin darkness and area of involvement was subjective.

CONCLUSION

Both oral and intralesional routes of tranexamic acid administration demonstrated high response rates in our study, although the differences observed were not statistically significant. These results align with existing literature, which reports comparable effectiveness for both routes in the treatment of melasma.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AM & MFS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MKA & NK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

TM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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