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Original Research Article

Comparison of efficacy of oral and topical route of tranexamic acid in patients of melasma

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ABSTRACT

Background: Melasma is a common pigmentary disorder which presents with brown coloured macules that occurs around the sun-exposed areas of the skin, particularly on the face. Many treatment modalities are present but often it is resistant to treatment. The aim of our study was to compare the therapeutic efficacy and safety of tranexamic acid administered by oral and topical route in patients of melasma.
Methods: Our study was a prospective, randomised study which consisted of 40 new melasma patients. 20 patients were given Oral Tranexamic acid 250 mg twice daily, classified as Group 1, other 20 patients were given topical Tranexamic acid (3%) twice a day (fully covering the lesion), classified as Group 2 for a period of 8 weeks and both were given broad spectrum sunscreen (SPF 50). MASI was determined before starting treatment (baseline), 4 weeks and 8 weeks. Based on the reduction in the mean MASI, the therapeutic response is graded and subjective response and adverse effects were also recorded at each visit.
Results: Mean percentage reduction in MASI scores was higher in oral (52.1%) as compared to topical (31.9%) group. In oral group, headache was the only adverse effect, however, in topical group, erythema, burning, acneiform eruptions were reported. At final assessment, fair improvement was seen in both groups.
Conclusions: Both oral as well as topical tranexamic acid were efficacious for treatment of melasma, however, of the two oral tranexamic acid was safer and provided a better proportional response.

Keywords: Melasma, Oral tranexamic acid, Topical tranexamic acid, MASI

INTRODUCTION

Melasma is an acquired, circumscribed, pigmentary disorder characterized by more or less symmetrically distributed, medium to dark brown macules with defined geographic borders, affecting the sun exposed areas, particularly the forehead, cheeks, temples and upper lip. It is common among darker individuals including Indians and more frequently among females.[1] Genetic predisposition, UV radiation exposure, hormonal factors such as female sex hormones and thyroid disease, pregnancy and drugs like phenytoin are known risk factors.[2]

On the basis of histological and Wood's lamp examination, it can be defined as epidermal, dermal or mixed type. In melasma, melanocytes are increased in activity, with an associated increase in the formation, size and melanization of melanosomes.

Major focus of treatment is sun protection and using sunscreens.[1,2] Various treatment modalities available include topical depigmenting agents like hydroquinone (2-4%), retinoic acid (0.1%) and fluorinated steroids, non-steroidal demelanizing creams (kojic and azelaic acid), superficial chemical peels (glycolic acid, trichloroacetic acid, and lactic acid), lasers (Q-switched Nd: YAG laser,

ruby laser, etc.) and intense pulsed light (IPL). Apart from hemostatic effects, Tranexamic acid also displays anti-inflammatory and antiallergic properties.[2]

Tranexamic acid

Tranexamic acid is a plasmin inhibitor used to prevent fibrinolysis to reduce blood loss. In addition, it is similar to tyrosine in its structure, which means that it can competitively inhibit the enzymatic activity of tyrosinase.[3] Increased levels of plasmin elevates α- MSH and fibroblast growth factor which are both potent melanocyte stimulators.[4] Tranexamic acid has been evaluated for the treatment of melasma in various formulations, including topical, intradermal, and oral.[5] Adverse effects include seizures, headaches, backache, abdominal pain, nausea, vomiting, diarrhea, fatigue, pulmonary embolism, deep vein thrombosis, anaphylaxis, impaired color vision and other visual disturbances.[6]

METHODS

After obtaining clearance from the Ethics committee, 40 new patients of melasma attending the Department of Dermatology, Era's Lucknow Medical College and Hospital were included in the study after obtaining written informed consent from the patients over the period of 8 months (11 May 2022 to 11 January 2023) to complete the sample size with all the follow up.

Inclusion criteria

Clinically diagnosed melasma patients, Age group between 18-50 years and Both male and female patients were included.

Exclusion criteria

Patients who took melasma therapy in the last 6 weeks. Patient with pre-existing bleeding, coagulation, thromboembolic or psychological disorders. Patient with history of hypersensitivity to tranexamic acid. Pregnant, lactating women or patients on oral contraceptives and Patients having any serious medical or surgical illness were excluded.

Procedure

Patients were randomly divided into two equal groups using sequentially numbered opaque sealed envelope (SNOSE) technique. Twenty patients each were allocated to two groups, 20 patients were given oral Tranexamic acid 250 mg twice daily along with broad spectrum sunscreen (SPF 50) these patients were classified as Group 1, other twenty patients were given topical Tranexamic acid (3%) twice a day (fully covering the lesion) along with broad spectrum sunscreen (SPF 50), these patients were classified as Group 2. They were followed up at 4 weeks and 8 weeks. Same sunscreen was used in both the groups.

All patients of melasma were clinically examined, during examination necessary demographic details, family history, past medical history, clinical history (duration, precipitating factors), general examination and cutaneous examination were recorded on a separate case sheet. Data was used for analysis to get the results aimed for. Patients were followed up at 4 and 8 weeks. MASI (Melasma area severity index) was determined before starting treatment (baseline) and at the end of 4 weeks and 8 weeks. Based on the reduction in the mean MASI, the therapeutic response is graded and subjective response was also taken into consideration.

It was graded as poor, fair, good and excellent with each corresponding to 0-25% improvement, 26-50% improvement, 51-75% improvement and 76-100% improvement respectively.[7] Adverse effects were noted at each visit. Analysis of data was done SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software on a computer. The values were represented in Number (%) and Mean±SD. Chi-square test was used to test the significance of categorical data and student 't' test was used to test the significance of two mean values. Level of significance was $p<0.05$. Other statistical tools were also applied when and wherever required.

RESULTS

The present study was conducted in the department of dermatology, Era's Lucknow medical college & hospitals, Lucknow to compare the therapeutic efficacy and safety of tranexamic acid administered by oral and topical route in patients of Melasma.

Table 1: Comparison of age profile of the patients in two study groups.

Characteristic	Group 1 (Oral), (N=20)		Group 2 (Topical), (N=20)		Statistical significance
Mean age±SD (years)	33.85±7.71		32.80±7.43		t=0.438; p=0.664
Age groups (years)	N	%	N	%	Chisquare=1.041; p=0.791
18-24	2	10.0	3	15.0	
25-34	10	50.0	8	40.0	
35-44	6	30.0	8	40.0	
45-50	2	10.0	1	5.0	

Table 2: Comparison of type of melasma in the two study groups.

Type of melasma	Group 1 (Oral) (N=20)		Group 2 (Topical) (N=20)		Statistical significance
	N	%	N	%	
Epidermal	16	80.0	17	85.0	Chisquare=1.030; p=0.597
Dermal	1	5.0	0	0.0	
Mixed	3	15.0	3	15.0	

Table 3: Comparison of MASI at baseline and different follow-upintervals between two study groups.

Time interval	Group 1 (Oral) (N=20)		Group 2 (Topical) (N=20)		Statistical significance (Independent Samples 't' test)
	Mean	SD	Mean	SD	
Baseline	10.85	6.73	11.45	5.35	t=0.312; p=0.757
Week 4	7.20	5.20	9.30	5.18	t=1.280; p=0.208
Final follow-up (8 weeks)	5.20	4.07	7.80	4.91	t=1.824; p=0.076
Within group change from baseline to final follow-up	-5.65±3.41 (-52.1%)		-3.65±1.53 (-31.9%)		-
Significance of within group change (Paired 't' test)	t=7.416; p<0.001		t=10.660; p<0.001		

Table 4: Comparison of subjective improvement between two studygroups at 4th Week follow-up.

Outcome	Group 1 (Oral) (N=20)		Group 2 (Topical) (N=20)	
	N	%	N	%
Poor	1	5.0	1	5.0
Fair	13	65.0	16	80.0
Good	5	25.0	3	15.0
Excellent	1	5.0	0	0.0

χ^2=1.810; p=0.613

Table 5: Comparison of subjective improvement between two studygroups at 8th Week follow-up.

Outcome	Group 1 (Oral) (N=20)		Group 2 (Topical) (N=20)	
	N	%	N	%
Poor	5	25.0	6	30.0
Fair	15	75.0	14	70.0
Good	0	0	0	0
Excellent	0	0	0	0

χ^2=0.125; p=0.723

Table 6: Comparison of adverse effect profile between two groups.

Adverse effect	Group 1 (Oral) (N=20) Frequency (%)	Group 2 (Topical) (N=20) Frequency (%)	P value (Fisher exact test)
Erythema	0	1 (5%)	1.000
Burning	0	6 (30.0%)	0.020
Hypopigmentation	0	0	-
Acneiform eruption	0	2 (10%)	0.487
Headache	2 (10%)	0	0.487
Thromboembolic events	0	0	-

A total of 40 diagnosed patients of Melasma fulfilling the inclusion criteria attending the department were included in the study. Age of patients enrolled in the study ranged between 21 to 50 years, difference in mean age of Group 1 (33.85±7.71 years) and Group 2 (32.80±7.43 years). Majority of patients in both the groups were aged 25-44 years (80% each). Out of 40 patients enrolled in the study 34 (85.0%) were females and rest 15% were male. In both

the groups majority of patients were females. Though proportion of males was higher in Group 2 as compared to Group 1 (25.0% vs. 5.0%) yet the difference was not found to be significant statistically. In majority of patients of Group 1 and Group 2 (90.0% and 60.0%) melasma was observed in Centrofacial region, in rest of the patients melasma was observed at malar region. In none of the case melasma was observed in mandibular region.

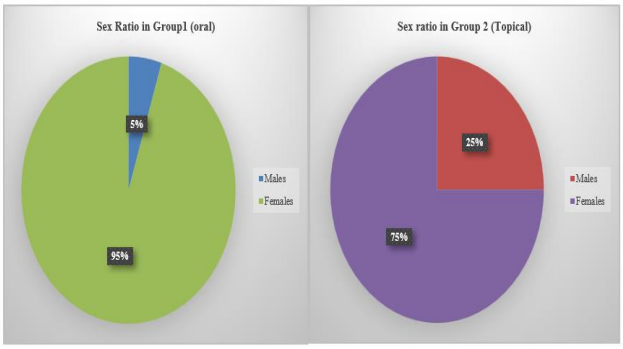

Figure 1: Comparison of sex of the patients in two study groups.

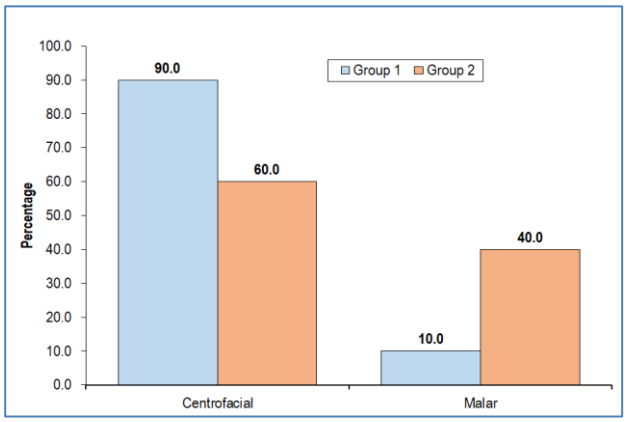

Figure 2: Comparison of distribution of melasma in two study groups.

Out of 40 patients enrolled in the study 34 (85.0%) were females and rest 15% were male. In both the groups majority of patients were females. Though proportion of males was higher in Group 2 as compared to Group 1 (25.0% vs. 5.0%) yet the difference was not found to be significant statistically. At baseline MASI score of Group 1 (10.85±6.73) was lower than that of Group 2 (11.45±5.35), when compared the difference was not found to be significant statistically. Similarly, at Week 4 MASI score of Group 1 (7.20±5.20) was lower than that of Group 2 (9.30±5.18). This difference too was not found to be significant statistically. At final follow up at 8 weeks, MASI score of Group 1 (5.20±4.07) was still lower than that of Group 2 (7.80±4.91) and this difference too was not found to be significant statistically. In both the groups statistically significant decline in baseline MASI score was observed. A decline of 5.65±3.41 in Group 1 and in Group 2 was 3.65±1.53. Percentage decline in baseline MASI score was higher in Group 1 as compared to Group 2 (52.1% & 31.9% respectively).

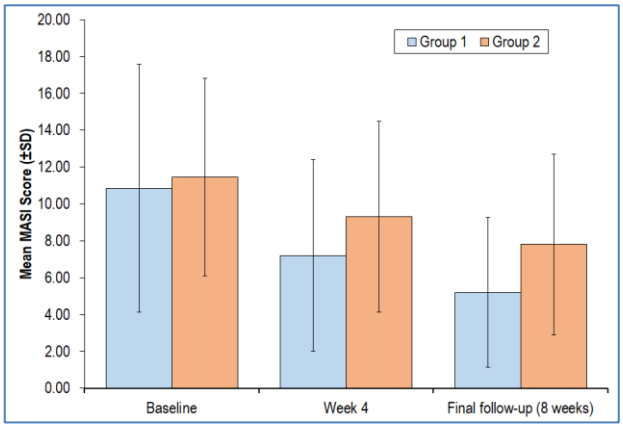

Figure 3: Comparison of MASI at baseline and at different follow up intervals.

At first follow up at 4 weeks after initiation of treatment, majority of patients of both the groups had Fair level of improvement (65.0% and 80.0%), only 5.0% of Group 1 patients had excellent level of improvement, 5.0% each patient of both the groups had poor improvement, rest of the patients (Group1: 25% & Group 2: 15.0%) had good improvement. Difference in level of improvement in two groups at first follow up was not found to be significant statistically. At final follow up, none of the patient had Good or Excellent level of improvement. Majority of patients of both the groups (75% & 70%) showed Fair improvement, rest showed Poor improvement. Difference in level of improvement at final follow up (8 weeks) in two groups was not found to be significant statistically. Hypopigmentation and thromboembolic events were not observed in any of the patient. In Group 1 only 2 (10%) patients reported headache as an adverse event. While in Group 2, Erythema (5%), Burning (30%), Acneiform eruption (10%) adverse effects had been reported. On comparing the incidence of adverse effects in two study groups, Burning was observed in significantly higher proportion of Group 2 cases (30.0% vs. 0.0%). Rest of the adverse effects did not show any significant between group differences in statistical terms.

DISCUSSION

Melasma is an acquired skin condition known for its chronicity and is clinically characterized by presence of hyperpigmented patches on the body areas exposed to ultraviolet radiation. It is one of the most common hyperpigmentation disorders and it is caused by hypermelanosis, i.e., due to excessive production of melanin by the melanocytes. The poor understanding of its pathogenesis makes it a rather unpredictable disease. Evidence has shown it to be more common in women in reproductive age years, often triggered by life events marked by natural or induced hormonal changes as a result of oral contraceptive use, pregnancy, genetic factors or due

to chronic inflammation of the skin and prolonged exposure to solar radiation.[8-10] Treatment of melasma is challenging owing to lack of proper knowledge regarding its etiopathogenesis, moreover it is highly refractive in nature and is marked by recurrences and low long-term efficacy of the treatment. The treatment strategies may include local as well as systemic therapies.

Tranexamic acid is one of the commonly used pharmacological agent that can be delivered through multiple routes. It can be used through oral, intravenous, intralesional and topical routes. Hence, the present study was planned to compare the therapeutic efficacy and safety of tranexamic acid administered by oral and topical route in patients of melasma. For this purpose, a prospective, comparative, randomized-controlled trial was carried out. In the present study we have used 250 mg twice daily as the suitable dose for oral and 3% TXA gel for topical routes. Although, TXA 250 mg twice a day is one of the most commonly used oral TXA regimen used in different studies, yet some workers have used other combinations too.[2,3,11-19] Nagaraju et al in their study used 500 mg twice daily dose.[19] Martinez et al in their study used 325 mg twice a day dose.[20] In another study Zhu et al compared four high dose drug combinations of 500 mg, 750 mg, 1000 mg or 1500 mg per day but found no significant difference among different dosages.[21] Thus, 500 mg/day (250 mg twice daily) is a suitable choice as a higher dose does not provide any additional treatment effect. With respect to the selection of topical drug dose, most of the previous studies also report use of 3% TXA.[15,22,23] Hence, the dose selection was in accordance with the previously used dose combinations that have been found to be safe as well as effective. The duration of treatment in the present study was 8 weeks. Some of the earlier studies have used treatment up to 12 weeks.[10,13,14,24,25] However, among those studies comparing oral and topical melasma, Na et al and Sahu et al similar to the present study carried out treatment for 8 weeks.[2,27] Malik et al on the other hand reported the treatment duration of 6 months.[16] Only a few other studies have reported treatment duration of 8 weeks.[8,24] The purpose to limit the treatment duration up to 8 weeks only was to avoid loss of follow-up. Moreover, the present study was instituted at the time of pandemic, when feasibility of longitudinal studies was doubtful in view of the looming threat of fresh waves. In the present study, majority of patients were females (85%). Na et al carried out their study on an exclusive female population.[8,24] In the study of Sahu et al too, most of the patients (91.7%) were females with males comprising only 8.3% of study population.[27] Owing to a direct relationship between female hormonal and melasma activity it is more commonly seen in females as compared to males with pregnancy being the most common risk factor. Melasma affects young women in reproductive age groups. As such, the age and sex profile of the patients in the present study was matched with most of the contemporary studies using oral or topical TXA for treatment of melasma. In the present study, mean MASI scores at baseline, week 4, and week8 were 10.85±6.73, 7.20±5.20 and 5.20±4.07 respectively in oral and 11.45±5.35, 9.30±5.18 and 7.80±4.91 respectively in topical groups. Overall, mean % reduction in MASI scores was higher in oral (52.1%) as compared to topical (31.9%) group. Oral TXA has been identified to produce a fast and substantial reduction in MASI scores. In the study by Tan et al the noted reduction was 66% which is slightly higher than that observed in the present study in the oral TXA group (52%) but could be attributed to a relatively longer treatment duration in their study (mean duration 3.7 months as compared to 8 weeks in the present study). In another study >75% reduction in MASI scores were seen in 25/39 (64.1%) of patients receiving oral TXA over a treatment duration of 12 weeks.[13] Sahu et al in their study found this reduction to be 25% only following 8 weeks of intervention. Compared to their study, the present study achieved a much better outcome in the same duration.[2]

As far as topical TXA is concerned, in the present study it produced a relatively lesser reduction in mean MASI scores (~32%). In the study by Sahu et al too topical treatment was able to produce much lesser improvement (5%).[2] The treatment response following 8 weeks of topical TXA treatment in the present study is similar to that reported by Kanechorn et al who foundnearly 44% reduction in MASI in the using topical 5% as compared to 3% TXA in the present study.[25] With respect to comparative performance, though we did not find a significant difference between oral and topical TXA groups either at baseline as well as at different follow-up intervals, however, the trend of a relatively better performance in the oral as compared to topical group is comparable to that reported by Sahu et al.[2] In the present study, there were no serious adverse events leading to cessation of treatment. In the oral group, headache was the only adverse effect reported in 2 (10%) cases, however, in topical group, erythema, burning, acneiform eruptions were reported in 5%, 30% and 10% patients respectively. Both topical as well as oral TXA have been found to be safe and free of any serious side effect in other studies too.[13,14]

Limitations

Some limitations of the study were small sample size, limitation ofintervention period to 8 weeks and absence of post-treatment follow-up to evaluate sustainability of results and relapse/recurrence assessment. However, despite these limitations, the present study found oral TXA to be as effective as topical TXA with a better safety profile and slight edge in terms of % improvement in mean MASI scores.

CONCLUSION

The present study was targeted to compare the oral Tranexamic acid to topical Tranexamic acid for treatment of melasma. For this purpose, a prospective, comparative, randomized-controlled study was carried out in which a total of 40 melasma patients (age range 21 to 50 years;

85% females) were enrolled and were randomized either to oral TXA group (250 mg twice a day) or topical TXA group (3% TXA gel, applied over the affected lesions twice daily) for a total duration of 8 weeks. Follow-up was conducted at 4 and 8 weeks. The key findings of the study were: The two groups were matched demographically for age, sex, marital status, occupation and place of residence. There was a dominance of centrofacial distribution (90%) in group 1 and (60%) in group 2, epidermal type (80%) in group 1 and (85%) in group 2 and symmetrical pattern (95%) in group 1 and (90%) in group 2. The two groups were comparable statistically for medical history, duration of illness, precipitating factors and type of melasma. Mean MASI scores at baseline, week 4, and week 8 were 10.85±6.73, 7.20±5.20 and 5.20±4.07 respectively in oral and 11.45±5.35, 9.30±5.18 and 7.80±4.91 respectively in topical groups. No significant difference was observed for MASI scores at different follow up intervals. Conclusion between two groups was observed for MASI scores at different follow-up intervals. Mean % reduction in MASI scores was higher in oral (52.1%) as compared to topical (31.9%) group. At final assessment, fair improvement was seen in 75% of oral and 70% of topical group patients, showing no significant difference between the two groups. In oral group, headache was the only adverse effect reported in 2 (10%) cases, however, in topical group, erythema, burning, acneiform eruptions were reported in 5%, 30% and 10% patients. The findings of the study showed that both oral as well as topical tranexamic acid were efficacious for treatment of melasma, however, of the two oral tranexamic acid was safer and provided a better proportional response.

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