Original Article

A Randomized Study to Evaluate the Efficacy of Oral Tranexamic Acid, Modified Kligman's Formula, and Placebo Cream in Melasma

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Abstract

Background: Despite the availability of various treatment modalities, the treatment of melasma is often incomplete, with a high recurrence rate. The present study was undertaken to assess the efficacy and safety of oral tranexamic acid (TXA), modified Kligman's formula (MKF), and a placebo cream in melasma. **Materials and Methods:** Ninety cases of melasma of both sexes were enrolled, and divided into three groups of 30 patients each. The baseline severity of melasma was graded by Melasma Area Severity Index (MASI) score. Group A, B, and C patients were treated with oral TXA 250 mg twice daily, daily MKF cream at night, and daily placebo cream at night, respectively, for 12 weeks. Improvement in MASI score was calculated after 4, 8, and 12 weeks. At each visit, adverse effects, if any, were noted. Statistical analysis was done using Chi-square test. **Results:** Based on intention to treat analysis, at the end of 12 weeks, the reduction in MASI score in oral TXA, MKF, and placebo groups was 9.94(65.91%), 6.12(54.78%), and 2.07(17.22%), respectively (P = 0.00). The difference in reduction of mean MASI scores after 12 weeks between oral TXA group and MKF group was not significant (P = 0.29). The efficacy of oral TXA and MKB was significantly higher than that of the placebo group (P = 0.01 and P = 0.03, respectively). Adverse effects in all groups were mild and self-limiting. **Limitations:** A limited sample size, non-blinded design, and absence of dermoscopic evaluation were the study limitations. **Conclusion:** In view of its excellent safety profile, oral TXA may be considered as a better option for moderate to severe melasma.

Keywords: *Melasma, modified Kligman's formula, oral tranexamic acid*

Introduction

Melasma is a common acquired, chronic, and relapsing pigmentary disorder that results in symmetrical, brownish facial pigmentation. Its prevalence ranges from 9% in Hispanic populations in the southern United States to 40% in southeast Asians and is cited as the most common pigmentary disorder in Indian women with a prevalence of 20–30% in the age group of 40–65 years.[1] Melasma has a significant impact on the quality of life and affects the social function and emotional state of the affected patients.[2,3] Melasma's intricate etiology, characterized by the interplay of genetic predisposition, hormonal fluctuations, and ultraviolet radiation exposure, has necessitated a nuanced and multi-faceted approach to treatment.[4]

Various treatment modalities used in melasma include topical hydroquinone (HQ), tretinoin, triple combinations, chemical peels like glycolic acid and lactic acid, intense pulsed light, and laser devices. The efficacy of these treatments is low, and treatment is incomplete with a high recurrence rate.[5] Tranexamic acid (TXA) is a derivative of amino acid lysine, which inhibits plasminogen activator and has demonstrated depigmenting properties and good efficacy in melasma.[6] Among topical preparations, the combination of 2% hydroquinone, 0.01% fluocinolone acetonide, and 0.025% tretinoin is the most accepted modified Kligman's formula (MKF), in wide use all over the world.[7] There is a paucity of studies assessing and comparing the efficacy of oral TXA and MKF used as monotherapy in melasma. Hence, in this background, the present study was undertaken to assess and compare the efficacy of oral TXA with MKF and a placebo cream in melasma.

Materials and Methods

The present study was carried out on 90 patients with melasma attending the

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dermatology out-patient department at a sub-urban medical college hospital. It was a prospective hospital-based randomized open-label therapeutic study carried out over a period of 18 months from December 2019 to May 2021 after being approved by the institutional ethics committee (88/2/18). The sample size was calculated using the study by Khurana *et al*.[6] The difference of means formula was used to determine the sample size, and the minimum difference considered between groups was 0.5. To achieve a power of study of 80% and a precision alpha of 0.05 with a 95% confidence interval (CI), the estimated sample size per group was determined to be 30.

Clinically diagnosed cases of melasma of both sexes with an age above 18 years were enrolled. Patients with defective color vision, coagulopathy, hypersensitivity, cardiovascular disease, and stroke, pregnant females, lactating females, and patients on anticoagulant medications were excluded. After taking informed consent, general demographic data regarding age, sex, and contact information were noted. Detailed history was taken regarding duration of disease, progression, history of hypothyroidism, history of previous drug intake, and family history of melasma. Thorough dermatological examination was done in all patients taking note of area of involvement and pattern of involvement. Woods lamp examination was done in all patients, and melasma was classified into epidermal, dermal, or mixed variant based on the findings. At the time of enrolment, patients were assessed clinically by a single trained dermatologist to grade the severity of melasma as per Melasma Area and Severity Index (MASI) score proposed by Kimbrough-Green *et al*.[8] The face was divided into four regions [forehead (F) 30%, right malar (MR) 30%, left malar (ML) 30%, chin (C) 10%], and each area was given a numerical value (A, 0–6). The sum of severity for darkness (D, 0–4) and homogeneity (H, 0–4) of melasma was multiplied by the numerical value and percentage of each area. These values were then added to obtain MASI by a single-blinded trained dermatologist.

MASI = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC

General physical examination and systemic examination were done, and laboratory investigations like complete blood count, thyroid profile, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) were done, and patients with deranged laboratory tests were excluded from the study. Patients were divided into three groups of 30 patients each: groups A, B, and C. The randomized table provided by a statistician for the generation of the randomization sequence was used for group allocation. Patients of all groups were advised to apply sunscreen with a sun protection factor (SPF) >30 three times during daytime at an interval of 3 hours.

Group A: Patients were advised to take oral TXA 250 mg twice daily for 12 weeks.

Group B: Patients were advised to use topical MKF consisting of hydroquinone 2%, tretinoin 0.025%, and flucinolone acetonide 0.01% at night over the affected area for 12 weeks.

Group C: Patients in this group constituted the control group and were advised to use emollient cream containing white soft paraffin at night over the affected areas for 12 weeks.

Patients in all groups were subjected to the respective treatment for 12 weeks with review visits at every 4 weeks. At each visit, photographic documentation was done and MASI score was calculated. Improvement in pigmentation and adverse effects, if any, were noted at each visit. In all groups, final grading of MASI score was done after 12 weeks. In patients who were administered oral TXA, laboratory tests for APTT, PT, and INR were done at the end of the study. Patients were followed up for 6 months after stopping the treatment at an interval of 3 months to determine the recurrence rate. The primary outcome measured was a decrease in post-treatment MASI score compared to baseline MASI score at the end of 12 weeks. The secondary outcome measured was adverse effects observed during the treatment period and recurrence of melasma during the follow-up period of 6 months.

Data collected from all patients were tabulated and analyzed. It was reported as mean or proportion, wherever appropriate. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 25. Chi-square test and analysis of variance (ANOVA) were used to calculate significant differences between parameters. Variables were considered significant for a confidence interval of 95% ($P < 0.05$). Effect sizes were also calculated in order to identify the magnitude of effect of the intervention regardless of the sample size; effect sizes exceeding 0.80 were considered large. Both intention to treat and per protocol analysis were done for all the variables.

Results

Details of the recruitment, allocation, and analysis of patients are shown in the patient flow diagram [Figure 1]. Baseline demographic and clinical characteristics of study subjects in the three groups were comparable [Table 1]. The age range spanned from 20 to 52 years, with a mean age of 33.39 years (SD = 3.41), and nearly half of the patients belonged to the 31–40 age group (n = 42, 46.66%). In the enrolled patients, MASI scores ranged from 1.2 to 37.2, with a mean MASI of 13.08 (SD = 1.96), with 42 patients (46.66%) eliciting a MASI score within 0–12. A total of 90 patients were recruited. Ten patients did not complete the 12-week treatment course, including two patients in the oral TXA group, three patients in the MKF group, and five patients in the placebo group. Out of these, seven patients (two in oral TXA group, two in MKF group,

Table 1: Baseline demographic and clinical profiles of study participants (*n*=90)

Characteristics	Group A (*n*=30)	Group B (*n*=30)	Group C (*n*=30)	*P*
Age (years)				
Mean±SD (Range)	34.39±3.40 (22-49)	36.13±3.97 (27-47)	33.73±2.90 (25-46)	0.62
Gender				
Female	26 (86.66%)	26 (86.66%)	25 (83.33%)	0.9
Male	4 (13.33%)	4 (13.33%)	5 (16.66%)	
Mean duration of disease (months)	19.55±2.5	18.67±2.2	18.10±2.9	0.16
Aggravating factor				
Thyroid disorders	4 (13.33%)	3 (10.0%)	3 (10.0%)	0.96
Positive family history	4 (13.33%)	5 (16.66%)	4 (13.33%)	
Drugs	1 (3.33%)	1 (3.33%)	1 (3.33%)	
Clinical pattern of melasma				
Centrofacial	17 (56.66%)	16 (53.3%)	15 (50.0%)	0.69
Malar	13 (43.33%)	14 (46.66%)	15 (50.0%)	
Mandibular	0	0	0	
Histological patterns				
Epidermal	13 (43.33%)	11 (36.66%)	12 (40.0%)	0.52
Dermal	8 (26.66%)	6 (20.0%)	7 (23.33%)	
Mixed	9 (30.0%)	13 (43.33%)	11 (36.66%)	
MASI score (mean)	15.88±8.69	11.99±8.59	12.27±5.49	0.07

SD - Standard deviation, MASI - Melasma area and severity index

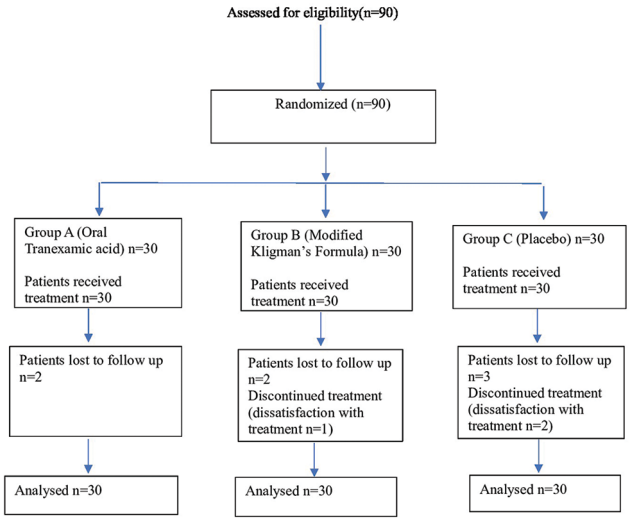

Figure 1: Patient flow diagram depicting total number of patients enrolled and considered for final analysis

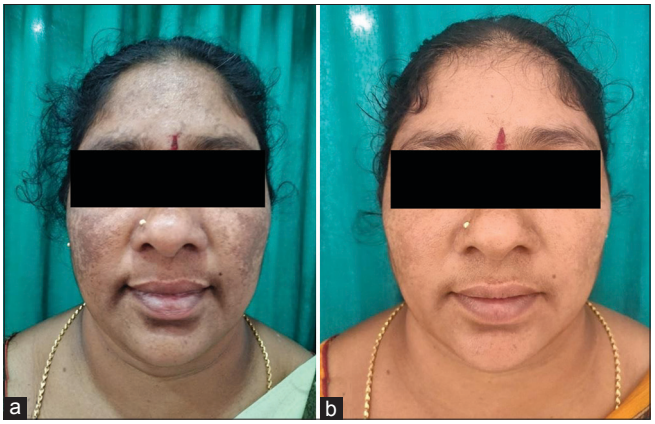

Figure 2: (a) Melasma over cheeks and forehead at baseline with MASI score of 16.4. (b) Marked improvement after 12 weeks of treatment with oral TXA showing reduction in MASI score to 3.16

and three in placebo group) were lost to follow-up, whereas three patients (one in MKF group and two in placebo group) were not satisfied with the treatment.

In group A patients who received oral TXA, statistically significant improvement in mean MASI score after 12 weeks of treatment was seen with both intention to treat analysis (9.94, $P = 0.00$) and per protocol analysis (10.04, $P = 0.00$) [Table 2, Figure 2]. In group B patients who received MKF, significant improvement in mean MASI score after 12 weeks of treatment was seen with both per protocol analysis (6.30, $P = 0.00$) and intention to treat analysis (6.12, $P = 0.00$) [Figure 3]. In group C, patients were advised to use placebo cream and an improvement in MASI score of 2.25 and 2.07 was observed on per protocol and intention to treat analysis, respectively ($P = 0.00$).

Based on intention to treat analysis, the evaluation of the intervention magnitude was considered large with the effect size being 0.80 and 0.83 (confidence interval 95%) at the end of 8 weeks and 12 weeks, respectively, when MASI scores were compared between groups A, B, and C ($P = 0.04$ and $P = 0.03$, respectively) [Table 3]. Notably, after 8 weeks, faster clinical improvement and a decrease in MASI score were achieved with oral TXA [7.24 (48.01%)] than MKF [4.15 (37.15%)] and placebo [1.78 (14.80%)] ($P = 0.04$). On per protocol analysis, on comparison of MASI scores between the three groups, large effect sizes of 0.82 and 0.86 (confidence

Table 2: Comparison of efficacy of oral TXA, modified Kligman's formula, and placebo cream after 4, 8, and 12 weeks with intragroup *P* value (intention to treat analysis, *n*=90 and per protocol analysis, *n*=80)

Treatment Group	Analysis	MASI at baseline	MASI after 4 weeks	MASI after 8 weeks	MASI after 12 weeks	Improvement in MASI score (%)	*P*
Oral TXA	Intention to treat (*n*=30)	15.08±8.12	11.01±7.27	7.84±4.78	5.14±4.42	9.94 (65.91%)	0.00
	Per protocol (*n*=28)	15.88±8.69	11.22±6.47	8.05±5.07	5.84±4.98	10.04 (63.22%)	0.00
MKF	Intention to treat (*n*=30)	11.17±6.48	9.06±6.39	7.02±5.64	5.05±5.46	6.12 (54.78%)	0.00
	Per protocol (*n*=27)	11.99±8.59	9.78±7.22	7.54±5.18	5.69±5.72	6.30 (52.54%)	0.00
Placebo cream	Intention to treat (*n*=30)	12.02±6.09	10.67±5.78	10.24±5.23	9.95±4.84	2.07 (17.22%)	0.00
	Per protocol (*n*=25)	12.27±5.49	10.77±7.34	10.36±6.38	10.02±6.22	2.25 (18.33%)	0.00

TXA – Tranexamic acid, MKF – Modified Kligman's formula

Table 3: Melasma area severity index – comparison between the 3 treatment groups at baseline, 4 weeks, 8 weeks, and 12 weeks with calculation of effect size (confidence interval – 95%, per protocol analysis, *n*=80 and intention to treat analysis, *n*=90)

	MASI at baseline	Effect size/*P*	MASI after 4 weeks	Effect size/*P*	MASI after 8 weeks	Effect size/*P*	MASI after 12 weeks	Effect size/*P*
Treatment group (per protocol analysis, *n*=80)								
Oral TXA (n=28)	15.88±8.69	0.29/0.07	11.22±6.47	0.37/0.197	8.05±5.07	0.82/0.04	5.84±4.98	0.86/0.02
MKF (*n*=27)	11.99±8.59		9.78±7.22		7.54±5.18		5.69±5.72	
Placebo cream (*n*=25)	12.27±5.49		10.77±7.34		10.36±6.38		10.02±6.22	
Treatment group (intention to treat analysis, *n*=90)								
Oral TXA (*n*=30)	15.08±8.12	0.27/0.06	11.01±7.27	0.38/0.24	7.84±4.78	0.80/0.04	5.14±4.42	0.83/0.03
MKF (*n*=30)	11.17±6.48		9.06±6.39		7.02±5.64		5.05±5.46	
Placebo cream (*n*=30)	12.02±6.09		10.67±5.78		10.24±5.23		9.95±4.84	

TXA – Tranexamic acid, MKF – Modified Kligman's formula

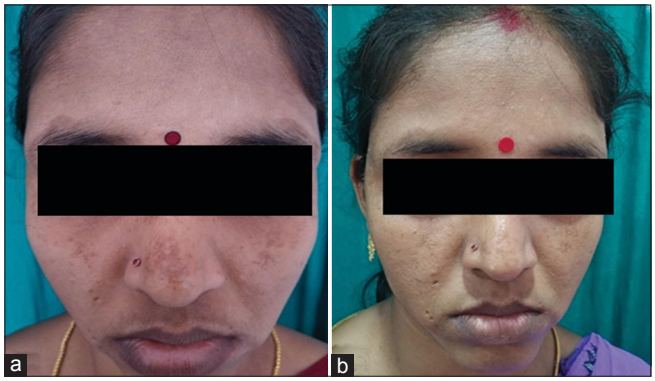

Figure 3: (a) Melasma over nose and cheeks at baseline; (b) Marked clinical improvement after 12 weeks of treatment with modified Kligman's formula

interval 95%) were obtained after 8 and 12 weeks of treatment. On comparison of efficacy of treatment between groups after 12 weeks, slightly higher reduction in MASI score with oral TXA than MKF was not significant (P = 0.29); however, both oral TXA and MKF demonstrated significantly higher efficacy compared to the placebo cream (P = 0.01 and 0.03, respectively).

Adverse effects were reported in seven patients (25%) in the oral TXA group with gastrointestinal intolerance seen in three patients (10.7%), headache in two patients (7.14%), and individual reports of pruritus (3.57%) and oligomenorrhea (3.57%). Laboratory tests for APTT, PT, and INR done at the end of the study showed normal values. No thromboembolic events were recorded. In the MKF group, 12 patients (44.44%) encountered adverse effects including erythema in six cases (22.22%) and irritant dermatitis and acne affecting three patients (11.11%) each.

In the present study, out of 80 patients who completed the study, recurrence was observed in 32 patients in the follow-up period of 6 months. The highest recurrence rate occurred in the placebo cream group, affecting 15 patients (60%), followed by 11 patients (39.28%) in the oral TXA group and 6 patients (22.22%) in the MKF group. The recurrence rate in all the three groups was statistically significant (P = 0.00).

Discussion

Several factors have been implicated in the pathogenesis of melasma including sun exposure, hormones, genetic influences, and vascular influences that cause melanocytes to become activated and produce excessive melanin in patients with melasma. Histological changes in lesional skin include increased melanocytes, melanosomes, solar elastosis, mast cells, blood vessels, and vascular endothelial growth factor, along with a disrupted and thinner basement membrane.[9,10] In spite of the availability of several treatment options including topical depigmenting agents,

chemical peels, and energy-based devices, many patients do not respond adequately, highlighting the pressing need for more effective treatments. MKF is one of the most commonly used and effective topical therapies in melasma. However, the topical corticosteroid component can promote undesirable adverse effects due to prolonged use.[11] Considering the multiple side effects of individual components of MKF, oral TXA may be a better treatment alternative if its efficacy matches that of MKF. Hence, this study was undertaken to compare the efficacy and safety of both the treatment options along with a placebo cream.

In the present study, only centrofacial and malar types of melasma were observed. Centrofacial melasma was more prevalent, affecting 48 patients (53.33%) , followed by malar type in 42 patients (46.66%). These findings were in discordance with the higher prevalence of malar melasma reported by Sahu *et al*.[12] (65%), Ahmad Nasrollahi *et al*.,[13] (72.74%) and Arreola Jauregui *et al*.[14] (52.83%). In our study, the baseline MASI scores ranged from 1.2 to 37.2, with a mean score of 13.08. The mean baseline MASI scores in studies done by Del Rosario *et al*.[15] and Bansal and Sardesai[16] were 8.52 and 4.24, respectively. The higher baseline MASI score in our study may be attributed to the higher occupational sun exposure observed in our patients who were predominantly rural outdoor workers.

In group A, patients received oral TXA at a dosage of 250 mg twice daily for 12 weeks in conjunction with regular sunscreen use. Based on per protocol analysis, in the 28 patients who completed the study, the mean MASI score at baseline was 15.88 (SD = 8.69), which decreased to 11.22, 8.05, and 5.84 after 4, 8, and 12 weeks, respectively (63.22% improvement) (P = 0.00). Previous studies by Wu *et al*.[17] and Aamir and Naseem,[18] which employed visual analog scale to assess treatment response of oral TXA in melasma, also reported marked clinical response emphasizing oral TXA's clinical efficacy. Notably, based on a decrease in MASI score (intention to treat), after 8 weeks of treatment, our study indicated a faster therapeutic effect (48.01%) with oral TXA than MKF (37.15%) and placebo (14.80%) (P = 0.04). Similar observations of faster improvement within the first 2 months of treatment were made by Li *et al*.[19] and Lee *et al*.[20] in previous Asian studies. TXA acts as a plasmin inhibitor and inhibits conversion of plasminogen to plasmin via the plasminogen activator. TXA inhibits UVR-induced activation of plasmin on the keratinocytes by preventing plasminogen's attachment on the keratinocytes, which in turn reduces arachidonic acid and prostaglandins, resulting in reduction in melanogenesis. Other mechanisms of action of TXA in melasma include decreasing tyrosinase activity in melanocytes, possibly by decreasing production of fibroblast growth factor, mast cell activity, and preventing angiogenesis by reducing vascular endothelial growth factor and endothelin 1, which are responsible for increased vascularity in melasma.[6,14] Use of oral TXA in melasma has been found to be safe in up to 6 months of use. Higher efficacy with synergistic action has been achieved with the use of oral TXA in combination with topical agents such as hydroquinone, MKF, and energy-based devices.[11]

In group B patients who received MKF cream along with sunscreen, intention to treat analysis showed that after 12 weeks, the MASI score showed a significant reduction from a baseline of 11.17 to 5.05 (54.78% improvement) (P = 0.00). This result is consistent with previous studies by Mahajan *et al*.[21] and Chan *et al*.,[22] who reported an improvement in MASI scores at 12 weeks of 52.90% and 64.2%, respectively. In view of the chronic nature of melasma, long-term treatment with MKF may be required. In India, topical preparations may be procured easily without prescription. Because of the above reasons, long-term use of Kligman's formula and its modifications can lead to adverse effects including hypertrichosis, telangiectasia, irritant dermatitis, and atrophy. In group C patients who were treated with placebo cream, based on per protocol, MASI scores decreased from a baseline of 12.27 to 10.02 after 12 weeks, resulting in an improvement of 2.25 (18.33%) (P = 0.00). The positive therapeutic response observed in this group can be attributed to the regular use of sunscreen as the emollient cream itself does not have any therapeutic effect. This aligns with findings from a study conducted by Sarkar *et al*.,[23] which explored the effectiveness of sunscreen in managing melasma and reported a 26.09% decrease in MASI score after 12 weeks.

On comparing the efficacy of all three modalities (per protocol), the difference in mean MASI scores after 12 weeks between oral TXA group and MKF group was not significant (P = 0.29). However, the efficacy of oral TXA and MKB was significantly higher than placebo group (P = 0.01 and P = 0.03, respectively). Bansal and Sardesai[16] and Sahu *et al*.[12] also reported comparable efficacy between MKF and oral TXA. In our study, recurrence rates differed among the treatment groups, with 11 patients (39.28%) experiencing recurrence in oral TXA group, six patients (22.22%) in MKF group, and a notably higher rate of 15 patients (60%) in placebo group. The time to recurrence varied, occurring within 1 to 6 months. Administration of protective rather than definitive active treatment could be the reason for limited improvement in MASI score and high recurrence in placebo group. These recurrence rates were consistent with previous studies reported by Del Rosario *et al*.[15] and Majid.[24] A longer course of therapy may be needed in patients with severe melasma, and further investigation into this possibility is warranted.

The most common adverse effect in oral TXA group was gastrointestinal discomfort with bloating in three patients (10.7%), followed by headaches in two patients (7.14%). Notably, laboratory tests for APTT, PT, and INR done after 12 weeks showed normal values.

All adverse effects were transient and self-limiting and did not result in stoppage of treatment. These results were consistent with previous studies by Lee *et al*.[20] and Padhi and Pradhan.[11] In patients treated with MKF, 12 patients (44.44%) experienced side effects, including erythema (22.22%), irritation (11.11%), and acne (11.11%). Potential modifications in treatment regimens, such as shorter durations, intermittent therapy with treatment-free intervals, and alternate-day MKF application, may help mitigate adverse reactions.[7]

Limitations

The study's limitations include a limited sample size, non-blinded design, and the absence of dermoscopic evaluation. The assessment of treatment response relied solely on the reduction in the MASI score, without considering other factors such as the melanin index. Additionally, for resistant and recalcitrant melasma cases, longer treatment duration and extended follow-up periods would be necessary.

Conclusion

Oral TXA and MKF demonstrated comparable efficacy in treating melasma. A faster therapeutic effect was achieved with oral TXA than MKF after 8 weeks of treatment. In view of its excellent safety profile and faster onset of action, oral TXA may be considered as a promising treatment option for moderate to severe melasma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hourblin V, Nouveau S, Roy N, de Lacharrière O. Skin complexion and pigmentary disorders in facial skin of 1204 women in 4 Indian cities. Indian J Dermatol Venereol Leprol 2014;80:395-401.
2. Raveendra L, Sidappa H, Shree S. A study of quality of life in patients with facial melanoses. Indian Dermatol Online J 2020;11:154-7.
3. Abolfotouh MA, Al-Khowailed MS, Suliman WE, Al-Turaif DA, Al-Bluwi E, Al-Kahtani HS. Quality of life in patients with skin diseases in central Saudi Arabia. Int J Gen Med 2012;5:633-42.
4. Sarkar R, Das A, Katoch S. Hyperpigmentary disorders. In: Sacchidanand S, Savitha AS, Shilpa K, Sashikumar BM editors. IADVL Text Book of Dermatology. 5th ed. Mumbai: Bhalani Publishing House 2022. p. 1473-518.
5. Sarkar R, Gokhale N, Godse K, Ailawadi P, Arya L, Sarma N, *et al*. Medical management of melasma: A review with consensus recommendations by Indian Pigmentary Expert Group. Indian J Dermatol 2017;62:558-77.
6. Khurana VK, Misri RR, Agarwal S, Thole AV, Kumar S, Anand T. A randomized, open-label, comparative study of oral tranexamic acid and tranexamic acid microinjections in patients with melasma. Indian J Dermatol Venereol Leprol 2019;85:39-43.
7. Grimes PE, Bhawan J, Guevara IL, Colón LE, Johnson LA, Gottschalk RW, *et al*. Continuous therapy followed by a maintenance therapy regimen with a triple combination cream for melasma. J Am Acad Dermatol 2010;62:962-7.
8. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, *et al*. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. Arch Dermatol 1994;130:727-33.
9. Achar A, Rathi SK. Melasma: A clinico-epidemiological study of 312 cases. Indian J Dermatol 2011;56:380-2.
10. Sheth VM, Pandya AG. Melasma: A comprehensive update: Part I. J Am Acad Dermatol 2011;65:689-97.
11. Padhi T, Pradhan S. Oral tranexamic acid with fluocinolone-based triple combination cream versus fluocinolone-based triple combination cream alone in melasma: An open labeled randomized comparative trial. Indian J Dermatol 2015;60:520-5.
12. Sahu PJ, Singh AL, Kulkarni S, Madke B, Saoji V, Jawade S. Study of oral tranexamic acid, topical tranexamic acid, and modified Kligman's regimen in treatment of melasma. J Cosmet Dermatol 2020;19:1456-62.
13. Ahmad Nasrollahi S, Sabet Nematzadeh M, Samadi A, Ayatollahi A, Yadangi S, Abels C, *et al*. Evaluation of the safety and efficacy of a triple combination cream (hydroquinone, tretinoin, and fluocinolone) for treatment of melasma in Middle Eastern skin. Clin Cosmet Investig Dermatol 2019;12:437-44.
14. Arreola Jauregui IE, Huerta Rivera G, Soria Orozco M, Meyer-Nava S, Paniagua Santos JE, López Zaldo JB, *et al*. Cross-sectional report on melasma among Hispanic patients: Evaluating the role of oral 100 tranexamic acid vs. oral tranexamic acid plus hydroquinone. J Am Acad Dermatol 2020;83:1457-8.
15. Del Rosario E, Florez-Pollack S, Zapata L Jr, Hernandez K, Tovar-Garza A, Rodrigues M, *et al*. Randomized, placebocontrolled, double-blind study of oral tranexamic acid in the treatment of moderate-to-severe melasma. J Am Acad Dermatol 2018;78:363-9.
16. Bansal A, Sardesai VR. Comparison of effectiveness of oral tranexamic acid with that of the topical modified Kligman's formula in the treatment of melasma. Indian J Drugs Dermatol 2019;5:100-3.
17. Wu S, Shi H, Wu H, Yan S, Guo J, Sun Y, *et al*. Treatment of melasma with oral administration of tranexamic acid. Aesthetic Plast Surg 2012;36:964-70.
18. Aamir S, Naseem R. Oral Tranexamic acid in treatment of melasma in Pakistani population: A pilot study. J Pak Assoc Dermatol 2016;24:198-203.
19. Li Y, Sun Q, He Z, Fu L, He C, Yan Y. Treatment of melasma with oral administration of compound tranexamic acid: A preliminary clinical trial. J Eur Acad Dermatol Venereol 2014;28:393-4.

20. Lee HC, Thng TGS, Goh CL. Oral tranexamic acid (TA) in the treatment of melasma: A retrospective analysis. J Am Acad Dermatol 2016;75:385-92.
21. Mahajan R, Kanwar AJ, Parsad D, Kumaran MS, Sharma R. Glycolic Acid Peels/Azelaic Acid 20% cream combination and low potency triple combination lead to similar reduction in melasma severity in ethnic skin: Results of a randomized controlled study. Indian J Dermatol 2015;60:147-52.
22. Chan R, Park KC, Lee MH, Lee ES, Chang SE, Leow YH, *et al*. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Br J Dermatol 2008;159:697-703.
23. Sarkar R, Ghunawat S, Narang I, Verma S, Garg VK, Dua R. Role of broad-spectrum sunscreen alone in the improvement of melasma area severity index (MASI) and Melasma Quality of Life Index in melasma. J Cosmet Dermatol 2019;18:1066-73.
24. Majid I. Mometasone-based triple combination therapy in melasma: Is it really safe? Indian J Dermatol 2010;55:359-62.