ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 07 | July - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARATIVE EFFICACY, SAFETY, AND TOLERABILITY OF ORAL TRANEXAMIC ACID VERSUS KLIGMAN FORMULA IN MODERATE-TO-SEVERE MELASMA: A PROSPECTIVE INTERVENTIONAL STUDY

Dermatology

Dr. Aastha Sharma* MD Resident, Department of Dermatology, Venereology and Leprosy, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Uttar Pradesh, India*Corresponding Author

Dr. Anurag Verma Professor, Department of Dermatology, Venereology and Leprosy, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Uttar Pradesh, India

Dr. Rupika Singh Professor and Head, Department of Dermatology, Venereology and Leprosy, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Uttar Pradesh, India

KEYWORDS

INTRODUCTION

Melasma is a common, acquired disorder of hyperpigmentation presenting as symmetric, brownish-to-grey macules predominantly on sun-exposed facial areas. It affects up to 30% of Indian women between the ages of 40 and 65 years, with an estimated global prevalence ranging from 1% in unselected populations to 50% in high-risk groups such as pregnant women [1,2]. Despite its benign clinical course, melasma exerts a considerable negative impact on health-related quality of life through psychosocial distress, social withdrawal, and diminished self-esteem [3,4]. The condition predominantly affects women, with a female-to-male ratio of approximately 9:1, and is more prevalent in individuals with darker Fitzpatrick skin phototypes (IV–VI) [5,6].

The pathogenesis is multifactorial, involving interactions among ultraviolet (UV) radiation, hormonal influences, genetic predisposition, dermal vascularity, and inflammatory mediators [7,8]. Elevated expression of stem cell factor (SCF) and its receptor c-kit in the dermis of melasma-affected skin highlights the key paracrine role of the dermis in driving epidermal hyperpigmentation [9]. Hormonal influences further promote melanocyte activation, explaining the strong association with pregnancy and oral contraceptive use [10]. Histologically, the mixed subtype is the most prevalent variant in South Asian populations [11].

Kligman formula (KF)—originally described as a combination of hydroquinone, a retinoid, and a corticosteroid—remains a benchmark prescription for moderate-to-severe melasma [12]. The triple combination mechanism offers synergistic depigmentation; however, prolonged use is limited by erythema, irritation, post-inflammatory hyperpigmentation (PIH), and steroid-related cutaneous atrophy [13,14]. Strict photoprotection with broad-spectrum sunscreen forms the cornerstone of any management protocol [15]. Oral tranexamic acid (TXA) has gained recognition as a systemic option, suppressing melanogenesis by inhibiting the plasminogen–plasmin system and attenuating dermal vascularity through VEGF downregulation [16-18]. At a dose of 250 mg twice daily, it has demonstrated an acceptable safety profile [19,20]. Head-to-head comparative data evaluating oral TXA against KF as monotherapy in Indian patients remain limited; hence, this study was undertaken [21,22].

Materials and Methods

This prospective, interventional, two-arm comparative clinical study was conducted over 24 months at the Department of Dermatology, Venereology and Leprosy, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, Uttar Pradesh, India. The study received institutional ethics committee approval, and written informed consent was obtained from all participants [23,24].

Adult female patients aged 18–45 years with a clinical diagnosis of moderate-to-severe melasma (MASI score ≥12) were eligible. Exclusion criteria included hypersensitivity, recent melasma treatment, anticoagulant therapy, thromboembolic history, oral contraceptive use, systemic illness, or pregnancy [25,26].

Forty patients were enrolled and randomly allocated into two groups of 20 each. Group A received KF (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01% cream) applied nightly along with a daytime broad-spectrum sunscreen (SPF ≥50). Group B received oral TXA 250 mg twice daily in addition to identical photoprotective measures. Follow-up evaluations were performed weekly for 12 weeks [27,28].

The primary outcome was absolute change in MASI score from baseline to week 12. Secondary outcomes included incidence of adverse effects, patient self-reported tolerability, and overall satisfaction [29,30]. Data analysis was performed using SPSS version 27.0. Continuous variables were compared using independent samples t-tests, categorical variables via chi-square tests, and within-group temporal changes via repeated-measures ANOVA. Statistical significance was set at $p < 0.05$ [31,32].

RESULTS

All 40 enrolled patients completed the 12-week study framework. Baseline demographic and clinical characteristics were highly comparable between both arms (Table 1). Mixed-type melasma was the most prevalent variant across the entire cohort (45% in each group).

Parameter	Group A – KF (n=20)	Group B – Oral TXA (n=20)	p-value
Mean age (years)	31.87 ± 6.22	32.14 ± 6.57	0.954
Mean melasma duration (years)	2.14 ± 1.21	2.35 ± 1.32	0.612
Married, n (%)	16 (80%)	17 (85%)	0.678
Outdoor occupation, n (%)	9 (45%)	10 (50%)	0.317
Melasma type – Mixed, n (%)	9 (45%)	9 (45%)	0.910
Melasma type – Epidermal, n (%)	7 (35%)	6 (30%)	-
Melasma type – Dermal, n (%)	4 (20%)	5 (25%)	-

Both treatment groups demonstrated statistically significant within-group reductions in MASI scores over 12 weeks (Group A: $F = 62.48$, $p < 0.0001$; Group B: $F = 31.92$, $p < 0.0001$). Intergroup comparisons revealed that Group A (KF) achieved significantly lower MASI scores at week 8 and week 12 compared to Group B (Table 2).

Visit	Group A – KF (mean ± SD)	Group B – Oral TXA (mean ± SD)	p-value (intergroup)
Baseline	18.42 ± 3.21	18.67 ± 3.10	0.801
Week 4	14.36 ± 2.98	15.89 ± 2.87	0.106
Week 8	10.72 ± 2.55	13.12 ± 2.76	0.007*
Week 12	7.85 ± 2.40	10.92 ± 2.85	0.0001*

Regarding clinical response, 20% of Group A achieved >75% improvement in MASI score compared with 5% in Group B. The overall incidence of adverse effects was significantly higher in Group A than Group B (40% vs. 15%; $p = 0.0036$), though Group A experienced purely local cutaneous reactions while Group B experienced mild systemic symptoms (Table 3).

Adverse Effect	Group A – KF, n (%)	Group B – Oral TXA, n (%)	p-value

Erythema	3 (15%)	0 (0%)	-
Burning / irritation	3 (15%)	0 (0%)	-
Post-inflammatory hyperpigmentation	2 (10%)	0 (0%)	-
Gastrointestinal symptoms	0 (0%)	2 (10%)	-
Menstrual irregularities	0 (0%)	1 (5%)	-
Overall adverse effects	8 (40%)	3 (15%)	0.0036*

Figure 1: Group A Pre And Post pictures of patient who received KF (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01% cream) applied nightly along with a daytime broad-spectrum sunscreen (SPF ≥50)

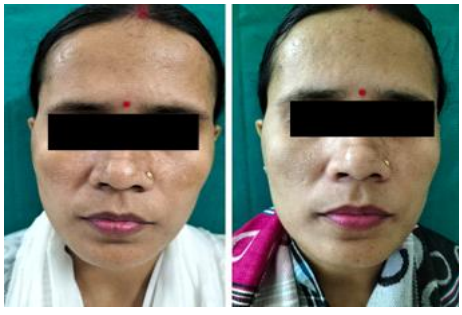

Figure 2: Group B pre and post pictures of patient who received oral TXA 250 mg twice daily in addition to identical photoprotective measures

DISCUSSION

This prospective comparative study evaluated oral TXA versus KF in 40 Indian women with moderate-to-severe melasma over 12 weeks. The principal finding is that both modalities produced significant and clinically relevant reductions in MASI scores; however, KF achieved statistically superior pigmentation clearance at weeks 8 and 12 [23,24]. The superior short-term efficacy of KF can be attributed to the synergistic action of its components: hydroquinone inhibits tyrosinase, tretinoin accelerates epidermal turnover, and the corticosteroid suppresses UV-induced prostaglandin-mediated inflammation [13,14].

Our findings align with Sahu et al. (2020), who reported greater absolute MASI reduction with a modified Kligman regimen compared with oral and topical TXA [23]. However, they contrast with Prathyoosha et al. (2024), who found higher MASI reduction for oral TXA over KF at 12 weeks [24]. Differences in specific formulations, study criteria, and patient baseline ranges may account for these variations. Importantly, oral TXA has been shown to offer valid therapeutic efficacy with high tolerability across diverse clinical settings [25,26].

The qualitative differences in safety profiles are critical. KF was tied strictly to local cutaneous reactions, whereas oral TXA induced mild systemic events (GI discomfort and menstrual irregularity), with zero thromboembolic incidents recorded [20,28]. Study limitations include a small sample size (n=40), a single-center design, a short 12-week follow-up window omitting long-term relapse monitoring, and the lack of standardized objective photography [29,30].

CONCLUSION

Both oral tranexamic acid and Kligman formula achieve clinically and statistically significant improvements in moderate-to-severe melasma over 12 weeks. Kligman formula demonstrates superior short-term efficacy in reducing MASI scores but carries a higher burden of local cutaneous reactions. Oral TXA represents a well-tolerated, effective systemic alternative with a distinct safety profile, making it particularly suitable for patients in whom prolonged topical corticosteroid exposure is undesirable.

Declarations

Ethical Approval: Granted by the Institutional Ethics Committee, Dr. KNS Memorial Institute of Medical Sciences, Barabanki, India.

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: None declared.
Funding: None.

REFERENCES

1. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. Indian J Dermatol. 2011;56(4):380–2.
2. 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(5):395–401.
3. Raveendra L, Sidappa H, Shree S. A study of quality of life in patients with facial melanoses. Indian Dermatol Online J. 2020;11(2):154–7.
4. Balkrishnan R, McMichael AJ, Camacho FT, et al. Development and validation of a health-related quality of life instrument for women with melasma. Br J Dermatol. 2003;149(3):572–7.
5. Sarkar R, Puri P, Jain RK, Singh A, Desai A. Melasma in men: a clinical, aetiological and histological study. J Eur Acad Dermatol Venereol. 2010;24(6):6-7.
6. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatol Venereol. 2013;27(2):151–6.
7. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. J Dermatol Sci. 2007;46(2):111–6.
8. Jo HY, Kim CK, Suh IB, et al. Co-localization of inducible nitric oxide synthase and phosphorylated Akt in the lesional skins of patients with melasma. J Dermatol. 2009;36(1):10–6.
9. Kang HY, Hwang JS, Lee JY, et al. The dermal stem cell factor and c-kit are overexpressed in melasma. Br J Dermatol. 2006;154(6):1094–9.
10. Jang YH, Lee JY, Kang HY, Lee ES, Kim YC. Oestrogen and progesterone receptor expression in melasma: an immunohistochemical analysis. J Eur Acad Dermatol Venereol. 2010;24(11):1312–6.
11. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL, Mihm MC Jr. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol. 1981;4(6):698–710.
12. Kligman AM, Willis I. A new formula for depigmenting human skin. Arch Dermatol. 1975;111(1):40–8.
13. Toralles MBP, Corrêa MP, Berbert Ferreira LM. Triple combination cream in the treatment of melasma: a systematic review of clinical trials. An Bras Dermatol. 2017;92(4):541–6.
14. Chan R, Park KC, Lee MH, et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Br J Dermatol. 2008;159(3):697–703.
15. Sarkar R, Ghunawat S, Narang I, Verma S, Garg VK. 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(4):1066–73.
16. Tse TW, Hui E. Tranexamic acid: an important adjuvant in the treatment of melasma. J Cosmet Dermatol. 2013;12(1):57–66.
17. Bala HR, Lee S, Wong C, Pandya AG, Rodrigues M. Oral tranexamic acid for the treatment of melasma: a review. Dermatol Surg. 2018;44(6):814–25.
18. Maeda K, Tomita Y. Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyte-conditioned medium. J Health Sci. 2007;53(4):389–97.
19. Leminen H, Hurskainen R. Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety. Int J Womens Health. 2012;4:413–21.
20. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and safety of tranexamic acid in melasma: a meta-analysis and systematic review. Acta Derm Venereol. 2017;97(7):776–81.
21. Pandya AG, Hynan LS, Bhore R, et al. Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. J Am Acad Dermatol. 2011;64(1):78–83.
22. Lee AY. Recent progress in melasma pathogenesis. Pigment Cell Melanoma Res. 2015;28(6):648–60.
23. Sahu PJ, Singh AL, Kulkarni S, et al. Study of oral tranexamic acid, topical tranexamic acid, and modified Kligman's regimen in treatment of melasma. J Cosmet Dermatol. 2020;19(6):1456–62.
24. Prathyoosha S, Ananditha K, Rao TN, Gopal KV, Raju PK. A randomized study to evaluate the efficacy of oral tranexamic acid, modified Kligman's formula, and placebo cream in melasma. Indian Dermatol Online J. 2024;15(5):787–93.
25. 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(2):100–3.
26. Khan MU, Khurshid K, Khan Z, et al. Comparative efficacy of oral tranexamic acid and Kligman's formula in the treatment of melasma: a randomized controlled trial. J Cosmet Dermatol. 2024;23(1):58–65.
27. Shin JU, Park J, Oh SH, Lee JH. Oral tranexamic acid enhances the efficacy of low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet laser treatment for melasma in Koreans: a randomized, prospective trial. Dermatol Surg. 2013;39(3 Pt 1):435–42.
28. Colferai MM, Miquelin GM, Steiner D. Evaluation of oral tranexamic acid in the treatment of melasma. J Cosmet Dermatol. 2019;18(5):1495–1501.
29. Chowdhary B, Mahajan VK, Mehta KS, et al. Therapeutic efficacy and safety of oral tranexamic acid 250 mg once a day versus 500 mg twice a day: a comparative study. Arch Dermatol Res. 2021;313(2):109–117.
30. Grimes PE, Yamada N, Bhawan J. Histological changes associated with long-term

topical triple combination treatment for melasma. J Am Acad Dermatol. 2005;52(5):863–70.
31. Rodrigues M, Pandya AG. Melasma: clinical diagnosis and management options. Australas J Dermatol. 2015;56(3):151–63.
32. Janney MS, Subramaniyan R, Dabas R, et al. A randomized controlled study comparing the efficacy of topical 5% tranexamic acid solution versus 3% hydroquinone cream in melasma. J Cutan Aesthet Surg. 2019;12(1):63–67.