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Original Research Article

Comparative Evaluation of Topical 30% Metformin Cream Versus Triple Combination Cream (Kligman's Formula) in the Treatment of Mixed Melasma

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Abstract: *Melasma is a chronic hyperpigmentation disorder characterized by irregular brown patches on sun-exposed areas of the face, causing significant cosmetic concern. The triple combination cream (Kligman's formula) is widely used as a standard treatment but often causes irritation and other side effects. Topical metformin, known for its anti-inflammatory and antioxidant effects, has emerged as a potential alternative therapy for melasma.* ***Objective:*** *To compare the efficacy and safety of topical 30% metformin cream versus triple combination cream (Kligman's formula) in the treatment of mixed melasma.* ***Methods:*** *This comparative study was conducted at the Department of Dermatology, CMH Gujranwala, from 1st Sep 2024 to 31st March 2025. A total of 140 patients diagnosed with mixed melasma were enrolled. Patients were assigned to receive either topical 30% metformin cream (Group A) or Kligman's formula (Group B) applied twice daily for 12 weeks. The Melasma Area and Severity Index (MASI) score was assessed at baseline, week 4, week 8, and week 12. Adverse effects and patient satisfaction were also recorded.* ***Results:*** *Both groups showed a significant reduction in MASI scores over 12 weeks. The mean percentage reduction in MASI was 50.6% in the metformin group and 60.2% in the Kligman's group ($p=0.001$). Adverse effects such as erythema, burning, and peeling were significantly lower in the metformin group ($p<0.05$). Patient satisfaction was comparable between groups.* ***Conclusion:*** *Topical 3% metformin cream is an effective and safer alternative to Kligman's formula for treating mixed melasma, with fewer side effects and satisfactory results.*

Keywords: Melasma, Metformin, Kligman's Formula, Hyperpigmentation, Topical Treatment

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Introduction

Melasma is a common acquired pigmentary disorder characterized by symmetrical hyperpigmented macules and patches, predominantly affecting sun-exposed areas of the face. (1) It is more prevalent in women, especially those of reproductive age, and individuals with darker skin phototypes (Fitzpatrick III–V). (2) The etiology of melasma is multifactorial, involving genetic predisposition, ultraviolet (UV) radiation exposure, hormonal influences (pregnancy, oral contraceptive use), and certain medications. (3) Clinically, melasma is classified into epidermal, dermal, and mixed types based on the depth of melanin deposition, with mixed melasma being the most challenging to treat due to the involvement of both epidermal and dermal pigment components. (4)

Kligman's formula, a triple combination cream comprising hydroquinone (a depigmenting agent), tretinoin (a retinoid), and a mild corticosteroid, remains the gold standard for melasma treatment. (5) It offers significant improvement by reducing melanin synthesis, promoting keratinocyte turnover, and inhibiting inflammation. However, long-term use is associated with adverse effects, including irritation, erythema, peeling, telangiectasia, and potential exogenous ochronosis, particularly with hydroquinone. (6,7)

Metformin, a biguanide-class oral hypoglycemic agent, has recently emerged as a promising topical treatment for melasma. Beyond its glucose-lowering effects, metformin exhibits notable anti-inflammatory, antioxidant, and anti-melanogenic properties. (8) It modulates key pathways such as the adenosine monophosphate-activated protein kinase (AMPK) pathway, thereby inhibiting melanogenesis and reducing melanin production. (9) Topical metformin has shown efficacy in suppressing melanin synthesis without the risks associated with hydroquinone and corticosteroids. (10) Preliminary studies on topical metformin, particularly at higher concentrations (30%), have demonstrated favorable outcomes in reducing pigmentation in melasma with minimal adverse effects. (11)

Despite these promising findings, there remains a lack of comparative studies evaluating the efficacy and safety of topical metformin compared with established treatment regimens, such as the triple combination cream. In particular, the role of 30% topical metformin cream in the management of mixed melasma, the most recalcitrant form, warrants further investigation. A comparative evaluation is crucial not only for determining the therapeutic equivalence or superiority of metformin but also for exploring its potential as a safer long-term alternative for patients intolerant to or unsatisfied with traditional agents. This study aims to compare the clinical efficacy, safety profile, and patient tolerability of topical 30% metformin cream with Kligman's formula in the treatment of mixed melasma. By analyzing changes in pigmentation, adverse effects, and overall treatment satisfaction, this research aims to provide evidence-based insights to optimize melasma management with potentially novel and safer therapeutic options.

Methodology

This comparative study was conducted at the Department of Dermatology, CMH Gujranwala, after getting approval from the Institutional Review Board (ERB No. 04/2024, Dated: 23-04-2024) from 1st Sep 2024 to 31st March 2025. A total of 140 patients clinically diagnosed with mixed melasma were enrolled after obtaining written informed consent. Sample size was calculated using OpenEpi software, with a confidence level of 95%, a power of 80%, and an anticipated effect size of 0.5 between the two treatment groups. (15) Patients were divided

into two equal groups of 70 each using a computer-generated randomization table.

Inclusion criteria included patients aged 20 to 50 years, of either gender, with clinically confirmed mixed-type melasma with a minimum duration of 3 months. Exclusion criteria were pregnancy, lactation, and hypersensitivity to any ingredient of the study formulations, history of hormonal therapy or systemic skin-lightening agents in the past three months, active facial dermatitis, and any concurrent dermatological condition affecting pigmentation.

Group A patients were treated with topical 30% metformin cream applied once daily at night. In comparison, Group B patients were treated with a triple combination cream (Kligman's formula containing 4% hydroquinone, 0.05% tretinoin, and 0.1% mometasone), applied once daily at night. All patients were instructed to use a broad-spectrum sunscreen with SPF 50 in the morning and to avoid excessive sun exposure during the study period. Patients were evaluated at baseline and every 2 weeks for up to 12 weeks for changes in pigmentation using the Melasma Area and Severity Index (MASI) score, along with documentation of any adverse effects. Efficacy was determined by comparing the reduction in MASI scores from baseline to 12 weeks, while safety was assessed by the frequency and severity of adverse reactions, including erythema, burning, dryness, and skin peeling. Patient satisfaction was evaluated at the end of the study using a 5-point Likert scale.

Data were analyzed using SPSS version 25. The mean and standard deviation were calculated for quantitative variables, while frequencies and percentages were computed for qualitative variables. Paired t-tests and independent sample t-tests were used to compare intra-group and inter-group MASI score reductions, respectively. At the same time, the Chi-square test was applied to compare categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

The mean age of patients in Group A (Metformin) was 34.6 ± 6.8 years, while in Group B (Kligman's) it was 35.2 ± 7.1 years. There were 18 (25.7%) males and 52 (74.3%) females in Group A, whereas Group B had 21 (30.0%) males and 49 (70.0%) females. The mean duration of melasma was 14.3 ± 4.2 months in Group A and 13.9 ± 4.7 months in Group B. The baseline MASI score was 16.4 ± 2.9 in the Metformin group and 16.1 ± 3.1 in the Kligman's group, as given in Table 1.

At baseline, the mean MASI score was 16.4 ± 2.9 in Group A (Metformin) and 16.1 ± 3.1 in Group B (Kligman's), with no significant difference between the groups. At week 4, the MASI score was reduced to 13.5 ± 2.7 in Group A and 12.9 ± 2.8 in Group B. By week 8, the scores further declined to 10.9 ± 2.6 in the Metformin group and 9.8 ± 2.4 in the Kligman's group, showing a statistically significant difference ($p = 0.02$). At week 12, the reduction was more pronounced, with Group A reaching 8.1 ± 2.4 and Group B reaching 6.4 ± 2.3, which was statistically significant ($p = 0.001$; see Table 2).

At 12 weeks, the mean percentage reduction in MASI score was 50.6 ± 8.4 in Group A (Metformin) and 60.2 ± 7.9 in Group B (Kligman's). The difference between the two groups was statistically significant ($p = 0.001$), with a greater reduction observed in Kligman's group. given in Table 3.

In Group A (Metformin), erythema was observed in 3 (4.3%) patients, burning sensation in 4 (5.7%), dryness in 5 (7.1%), and peeling in 2 (2.9%), while 56 (80%) patients reported no side effects. In contrast, Group B (Kligman's) showed higher frequencies of adverse effects, with erythema in 12 (17.1%), burning sensation in 18 (25.7%), dryness in 15 (21.4%), and peeling in 9 (12.9%), while only 33 (47.1%) patients reported no side effects, as shown in table 4.

Table 1: Baseline Demographic Characteristics of the Study Population (n = 140)

Characteristic	Group A (Metformin) n = 70	Group B (Kligman's) n = 70	p-value
Age	34.6 ± 6.8	35.2 ± 7.1	0.58
Gender			
Male	18 (25.7%)	21 (30.0%)	
Female	52 (74.3%)	49 (70.0%)	0.56
Duration of Melasma	14.3 ± 4.2	13.9 ± 4.7	0.61
Baseline MASI Score	16.4 ± 2.9	16.1 ± 3.1	0.48

Table 2: Mean MASI Score Reduction Over 12 Weeks

Time Point	Group A (Metformin) MASI (Mean ± SD)	Group B (Kligman's) MASI (Mean ± SD)	p-value
Baseline	16.4 ± 2.9	16.1 ± 3.1	0.48
Week 4	13.5 ± 2.7	12.9 ± 2.8	0.23
Week 8	10.9 ± 2.6	9.8 ± 2.4	0.02
Week 12	8.1 ± 2.4	6.4 ± 2.3	0.001

Table 3: Mean Percentage Reduction in MASI Score at 12 Weeks

Group	Mean Percentage Reduction (%)	p-value
Metformin (Group A)	50.6±8.4	0.001
Kligman's (Group B)	60.2±7.9	

Table 4: Frequency of Adverse Effects in Both Groups

Adverse Effect	Group A (Metformin)	Group B (Kligman's)	p-value
Erythema	3 (4.3%)	12 (17.1%)	0.01
Burning Sensation	4 (5.7%)	18 (25.7%)	0.002
Dryness	5 (7.1%)	15 (21.4%)	0.01
Peeling	2 (2.9%)	9 (12.9%)	0.03
No Side Effects	56 (80%)	33 (47.1%)	<0.001

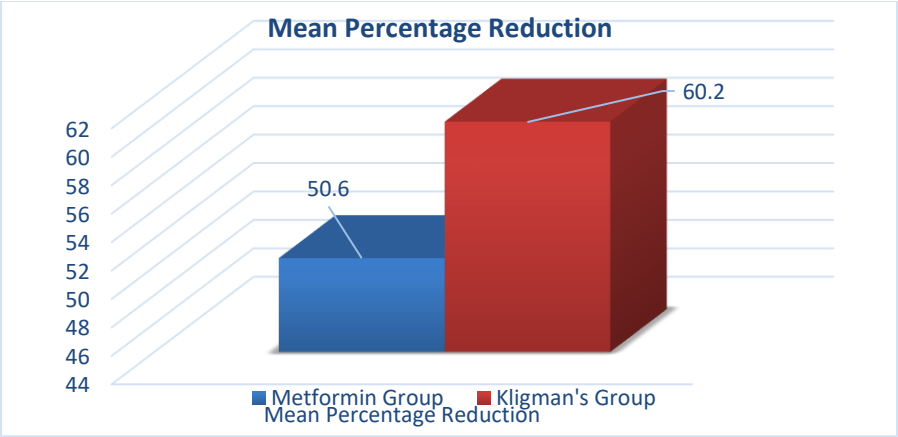

Figure 1: Mean Percentage Reduction in MASI Score at 12 Weeks

Discussion

Melasma is a common acquired hyperpigmentation disorder that predominantly affects women and individuals with darker skin types. It often appears as symmetrical brown patches on sun-exposed areas of the face, significantly impacting quality of life. (12) The pathogenesis involves multiple factors, including UV exposure, hormonal changes, and genetic predisposition. Kligman's formula, a triple combination cream, has long been considered a standard treatment but is associated with frequent side effects. (13) Topical metformin, an insulin-sensitizing agent with anti-inflammatory and antioxidant properties, has shown emerging promise in melasma management. (14) This study compares the efficacy and safety of 30% topical metformin cream with Kligman's formula in treating mixed melasma.

Our results demonstrated a mean percentage MASI reduction of 50.6% with metformin and 60.2% with Kligman's cream (p=0.001), indicating superior efficacy of Kligman's formula, which is in line with Hussain et al. (2024) who reported 60.28% reduction for metformin and 55.02% for hydroquinone with no significant difference in adverse effects. (15) Similarly, AboAlsoud et al. (2022) observed significant reductions in MASI scores with both treatments, though without significant differences between groups, supporting the comparable effectiveness of these agents. (16)

Our study findings are consistent with several previously published studies comparing topical metformin and Kligman's formula in the treatment of melasma. The mean age of patients in our study was 34.6 ± 6.8 years for the metformin group and 35.2 ± 7.1 years for the Kligman's group, which closely aligns with the demographics reported by Asadullah et al. (2024), who found mean ages of 35.95 ± 7.17 and 38.85 ± 7.80 years, respectively, with a predominantly female population in both groups. (17)

In terms of safety, our study found significantly fewer adverse effects in the metformin group, such as erythema (4.3% vs. 17.1%) and burning sensation (5.7% vs. 25.7%), which concurs with the meta-analysis by Mongkhon et al. (2023), where topical metformin had fewer side effects compared to the triple combination cream. (19) This improved safety profile makes metformin a promising alternative, especially for patients intolerant to the side effects of Kligman's formula. Kamal et al. (2020) and Bilal et al. (2022) also reported higher patient tolerance with metformin-based treatments, consistent with our findings. (18,20)

Moreover, the reduction in MASI scores over 12 weeks in our study confirms the efficacy trend reported by Asadullah et al. (2024), in which metformin showed a higher response rate (98.4%) than Kligman's (90.2%). (17) Our findings reinforce the potential role of topical metformin as a safer, effective treatment for mixed melasma, while Kligman's formula remains more potent but with a higher side effect burden. These results highlight the importance of individualized treatment selection that balances efficacy and tolerability.

This study was strengthened by its randomized design, adequate sample size of 140 participants, and standardized MASI score assessments over 12 weeks. Both male and female patients were included, enhancing generalizability. The comparison of a novel treatment (metformin cream) with a standard formulation (Kligman's) provided clinically relevant insights. However, limitations included the relatively short follow-up duration, which may not reflect long-term outcomes or recurrence rates. Patient-reported outcomes and quality-of-life measures were not assessed. Also, compliance and environmental exposures were not strictly controlled.

Conclusion

Topical metformin cream demonstrated significant improvement in melasma with fewer adverse effects. Kligman's formula showed superior efficacy but with a higher frequency of side effects. Metformin may offer a safer alternative for patients who are intolerant of conventional treatments.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-CMH-03211-24)

Consent for publication

Approved

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Not applicable

Conflict of interest

The authors declared no conflicts of interest.

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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