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Original Research Article

Efficacy of Topical 10% Isoniazid Cream Versus Triple Combination Cream (Kligman's Formula) in the Treatment of Mixed Melasma

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Abstract: *Melasma is an acquired pigmentary skin disorder characterized by symmetrical brown patches, most commonly on the face. The standard treatment involves topical triple-combination cream (Kligman's formula), but prolonged use is associated with adverse effects.* ***Objectives:*** *To compare the efficacy and safety of topical 10% isoniazid cream versus triple combination cream in the treatment of mixed melasma.* ***Methods:*** *This study was conducted at the Department of Dermatology, CMH Gujranwala, from 1st Sep 2024 to 31st March 2025. A total of 140 patients clinically diagnosed with mixed melasma were randomized into two groups of 70 each. Group A received 10% isoniazid cream, and Group B received the standard triple-combination cream, applied once daily at night for 8 weeks. Both groups used broad-spectrum sunscreen during the day. Efficacy was assessed using the modified Melasma Area and Severity Index (mMASI) and the physician global assessment (PGA). Adverse effects were also recorded.* ***Results:*** *Group A showed a greater mean reduction in mMASI score (5.7 ± 1.4) than Group B (4.4 ± 1.6), with a significant p-value (0.001). Excellent improvement (≥75%) was achieved in 40.0% of Group A, compared with 22.9% in Group B. Fewer adverse effects were reported in the isoniazid group.* ***Conclusion:*** *Topical 10% isoniazid cream was more effective and better tolerated than the triple combination cream for managing mixed melasma.*

Keywords: Adverse effects, Hyperpigmentation, Isoniazid, Kligman's formula, Melasma, Skin lightening, Topical therapy, Triple combination

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Introduction

Melasma is a chronic, relapsing, and commonly acquired pigmentary disorder that primarily affects sun-exposed areas of the face. (1) It is characterized by symmetric, irregular, brown to grayish-brown patches on the cheeks, forehead, upper lip, and chin. (2) Although melasma affects both genders, it is more prevalent among women, particularly those with darker skin phototypes (Fitzpatrick types III to V) and those residing in regions with high ultraviolet (UV) exposure. (3) The pathogenesis of melasma is multifactorial, involving genetic predisposition, ultraviolet radiation, hormonal influences (particularly estrogen and progesterone), pregnancy, use of oral contraceptives, thyroid dysfunction, and certain medications and cosmetics. (4) On histopathological grounds, melasma is commonly classified into three types: epidermal, dermal, and mixed, with mixed melasma being the most prevalent and challenging to treat due to the involvement of both the epidermis and dermis. (5)

Over the decades, various treatment modalities have been employed to manage melasma, including topical depigmenting agents, chemical peels, laser therapy, and photoprotection. Among these, the triple combination cream (Kligman's formula), which includes hydroquinone (a melanin synthesis inhibitor), tretinoin (a keratolytic agent), and a corticosteroid (an anti-inflammatory agent), remains the most widely prescribed and studied topical treatment for melasma. It is considered the gold standard due to its synergistic efficacy. (6)

Isoniazid, traditionally used as a first-line anti-tubercular drug, has recently drawn attention for its potential dermatological applications. Isoniazid inhibits mycobacterial cell wall synthesis by interfering with mycolic acid biosynthesis. Still, recent studies suggest it may also inhibit melanogenesis by targeting tyrosinase, a key enzyme in melanin production. (7) Preclinical investigations have revealed that isoniazid can reduce melanin synthesis without causing cellular toxicity or inflammation, making it a promising candidate for hyperpigmentation disorders such as melasma.(8,9,10)

Despite its theoretical benefits, clinical evidence on the use of topical isoniazid in melasma remains limited. Few pilot studies and case reports have demonstrated favorable outcomes with minimal adverse reactions, suggesting its utility as an emerging depigmenting agent. This study aims to compare the efficacy of topical 10% isoniazid cream with that of the triple combination cream (Kligman's formula) in the treatment of mixed melasma. By assessing improvements in pigmentation and adverse effects, this research will provide insight into whether isoniazid can serve as a viable alternative to current standard therapy. The findings could broaden clinicians' therapeutic options and potentially offer a safer, cost-effective solution for patients suffering from this challenging dermatological condition.

Methodology

After approval from the Institutional Review Board (ERB No. 04/2024, Dated: 23-04-2024), this randomized controlled trial was conducted at the Department of Dermatology, CMH Gujranwala, over a period of six months from 1st Sep 2024 to 31st March 2025. A total of 140 patients diagnosed clinically with mixed melasma were included in the study through non-probability consecutive sampling. The sample size was calculated using OpenEpi software, with a 95% confidence interval, 80% power, and an expected efficacy of 65% in the triple combination group and 83% in the isoniazid group. (15)

Patients of either gender, aged 18–50 years, with Fitzpatrick skin types III to V, and a clinical diagnosis of mixed melasma confirmed by Wood's lamp examination were included. Patients with a history of hypersensitivity to any component of the trial medications, active facial dermatoses, pregnancy, lactation, use of systemic or topical depigmenting agents within the last four weeks, or those undergoing concurrent

cosmetic procedures were excluded. After obtaining informed written consent, the enrolled patients were randomized into two equal groups of 70 each using a computer-generated random number table. Group A was treated with topical 10% isoniazid cream, while Group B received the standard triple combination cream (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%). Both groups were instructed to apply a pea-sized amount of the assigned cream to the affected facial areas once daily at night for 8 weeks. All patients were also advised to use a broad-spectrum sunscreen (SPF ≥ 30) during daytime and to avoid unnecessary sun exposure.

Baseline demographic data, including age, gender, duration of melasma, and Fitzpatrick skin type, were recorded. The severity of melasma was assessed using the modified Melasma Area and Severity Index (mMASI) score at baseline and at the end of the 8th week. Photographic documentation under standardized lighting conditions was also performed for comparative analysis. The primary outcome was the reduction in mMASI score from baseline to 8 weeks. Secondary outcomes included physician global assessment (PGA) and incidence of adverse effects such as erythema, scaling, burning, or irritation. All evaluations were performed by a blinded dermatologist who was unaware of group allocation.

Data were analyzed using SPSS version 25.0. Quantitative variables, such as age and mMASI scores, were presented as mean ± standard deviation and compared using paired and independent-samples t-tests, as appropriate. Categorical variables such as gender, Fitzpatrick skin type, and adverse effects were presented as frequencies and percentages, and compared using Chi-square or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 shows the baseline demographic and clinical characteristics of the study participants. The mean age of patients in Group A (10% isoniazid) was 33.4 ± 6.8 years, and in Group B (triple combination), 32.9 ± 7.1 years, with no significant difference between the groups (p = 0.642). Female patients predominated in both groups, comprising 85.7% in Group A and 88.6% in Group B. The average duration of melasma was similar between groups, with 18.2 ± 7.6 months in the isoniazid group and 17.6 ± 6.9 months in the triple combination group (p = 0.538). Most patients belonged to Fitzpatrick skin type IV in both groups, and no statistically significant differences were observed in baseline skin type distribution. This indicates that both groups were comparable at baseline with respect to age, gender, disease duration, and skin type.

Table 2 presents the comparison of modified Melasma Area and Severity Index (mMASI) scores before and after 8 weeks of treatment. Both groups had similar baseline mMASI scores (9.8 ± 2.1 in Group A vs. 9.6 ± 2.0 in Group B; p = 0.513). After 8 weeks, Group A showed a significantly greater reduction in mMASI score (5.7 ± 1.4) than Group B (4.4 ± 1.6), with a statistically significant difference (p = 0.001). This suggests that 10% isoniazid cream was more effective in reducing melasma severity over the 8-week treatment period.

Table 3 highlights the physician global assessment (PGA) at the end of 8 weeks. In Group A, 40.0% of patients achieved excellent improvement (≥75% reduction in pigmentation), compared to 22.9% in Group B. A good response (50–74% improvement) was observed in 37.1% of Group A and 41.4% of Group B. Fair and poor responses were more common in the triple combination group. The distribution of PGA outcomes differed significantly between groups (p = 0.021), indicating a superior clinical response in the isoniazid group.

Table 4 summarizes the adverse effects reported during the treatment period. Group B (triple combination) showed a significantly higher frequency of erythema (25.7% vs. 8.6%, p = 0.006), burning sensation (30.0% vs. 7.1%, p < 0.001), scaling (21.4% vs. 5.7%, p = 0.004), and irritation (14.3% vs. 4.3%, p = 0.044). Notably, 74.3% of patients in the isoniazid group reported no side effects, compared to only 30.0% in the triple combination group, with a highly significant p-value (p < 0.001). These findings indicate that topical 10% isoniazid was much better tolerated and associated with fewer adverse effects than the standard triple combination.

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

Variable	Group A (10% Isoniazid)	Group B (Triple Combination)	p-value
Age (years)	33.4 ± 6.8	32.9 ± 7.1	0.642
Gender			
Male	10 (14.3%)	8 (11.4%)	0.612
Female	60 (85.7%)	62 (88.6%)	
Duration of Melasma (months)	18.2 ± 7.6	17.6 ± 6.9	0.538
Fitzpatrick Skin Type			
Type III	16 (22.9%)	18 (25.7%)	0.721
Type IV	39 (55.7%)	38 (54.3%)	
Type V	15 (21.4%)	14 (20.0%)	

Table 2: Comparison of mMASI Scores Between Groups

Time Point	Group A (10% Isoniazid)	Group B (Triple Combination)	p-value
Baseline mMASI	9.8 ± 2.1	9.6 ± 2.0	0.513
Week 8 mMASI	4.1 ± 1.7	5.2 ± 2.1	0.001
Mean Reduction	5.7 ± 1.4	4.4 ± 1.6	0.001

Table 3: Physician Global Assessment (PGA) at Week 8

PGA Outcome	Group A (n = 70)	Group B (n = 70)	p-value
Excellent (≥75% improvement)	28 (40.0%)	16 (22.9%)	0.021
Good (50–74%)	26 (37.1%)	29 (41.4%)	
Fair (25–49%)	12 (17.1%)	18 (25.7%)	
Poor (<25%)	4 (5.7%)	7 (10.0%)	

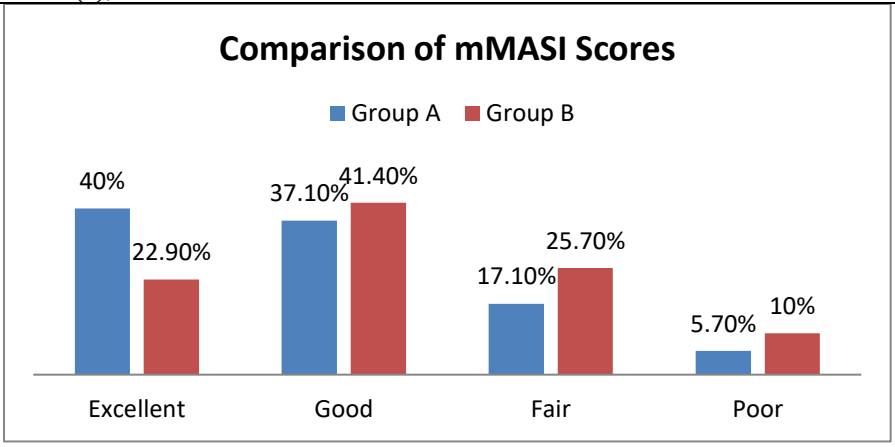

Figure 1: Physician Global Assessment (PGA) at Week 8

Table 4: Adverse Effects Observed During Treatment

Adverse Effect	Group A (n = 70)	Group B (n = 70)	p-value
Erythema	6 (8.6%)	18 (25.7%)	0.006
Burning Sensation	5 (7.1%)	21 (30.0%)	<0.001
Scaling	4 (5.7%)	15 (21.4%)	0.004
Irritation	3 (4.3%)	10 (14.3%)	0.044
No Side Effects	52 (74.3%)	21 (30.0%)	<0.001

Discussion

Melasma is a common pigmentary disorder causing symmetrical facial hyperpigmentation, predominantly affecting women of reproductive age. It significantly impacts quality of life due to its chronic and relapsing nature. (11) The most commonly used treatment, triple combination cream (Kligman's formula), though effective, is associated with several side effects. There is a growing demand for alternative therapies with comparable efficacy and fewer adverse reactions. (12) Isoniazid, an anti-tubercular agent, has shown potential depigmenting effects by inhibiting melanogenesis. (13) This study compares the efficacy and safety of 10% isoniazid cream with the triple combination in treating mixed melasma.

The present randomized controlled trial demonstrated that topical 10% isoniazid cream was significantly more effective and better tolerated than the standard triple combination cream (Kligman's formula) in the treatment of mixed melasma. Our findings align closely with those of Ahramiyanpour et al. (2024), who reported a reduction in mMASI score from 5.63 ± 3.28 to 2.13 ± 1.71 ($p = 0.002$) and a decrease in melanin index from 63.77 ± 6.27 to 55.92 ± 5.79 ($p = 0.001$) using 10% isoniazid over 12 weeks, with minimal side effects. (14) Similarly, in our study, the mean reduction in mMASI score was significantly higher in the isoniazid group (5.7 ± 1.4) compared to the triple combination group (4.4 ± 1.6), with a p-value of 0.001. Additionally, 40.0% of patients in the isoniazid group achieved excellent improvement, compared to 22.9% in the triple combination group. Compared to Asadullah et al. (2024), who observed a higher response rate in the TAM group (98.4%) versus Kligman's group (90.2%) and noted better mean MASI score reduction in the TAM group over 8 weeks, our findings are consistent in demonstrating the superiority of an alternative topical agent over the triple combination. (15) While our study did not reach a response rate as high as TAM's 98.4%, the clinical improvement in the isoniazid group was nonetheless statistically and clinically significant.

Bertold et al. (2023) compared a novel topical combination (NT) with Kligman's trio. They found a mean mMASI reduction of –4.33 (SE 0.71) in the NT group versus –2.84 (SE 0.69) in the Kligman group, with improvements in MelasQoL scores of –12.57 vs. –6.66, respectively. Although their p-value for mMASI was 0.14, indicating statistical insignificance, the trend still favors the novel therapy, reinforcing our finding that alternative agents, such as isoniazid, may provide superior outcomes in pigment clearance and quality of life. (16) Basit et al. (2021) compared oral tranexamic acid combined with triple combination versus triple combination alone and found a mean MASI score reduction of 6.49 ± 4.38 vs. 5.78 ± 5.04 ($p = 0.56$). This statistically insignificant difference contrasts with our study's results, in which isoniazid showed a clearly superior effect over the triple combination, with a significant p-value of 0.001. (17) Kamal et al. (2020) reported that 94.38% of patients treated with a newer regimen and 79.77% in the triple combination group showed clinical improvement, again aligning with our results, which showed a higher rate of excellent and good responses in the isoniazid group. (18)

Colón et al. (2008) investigated a sequential treatment regimen combining TC cream and glycolic acid peels. They found that 65% of participants achieved "treatment success" by week 12, and over 90% showed some level of improvement. (19) These outcomes support our findings by demonstrating that innovative or combination-based approaches often yield higher efficacy than monotherapy with triple combination. Akhtar et al. (2024) further reported that group B, which showed a greater reduction in MASI score (8.91 ± 2.42) than group A (7.05 ± 4.05), demonstrated a statistically significant improvement ($p = 0.010$). (20) These values indicate that alternative therapies can achieve superior clinical results when compared to traditional regimens. Our results, showing greater mMASI reduction in the isoniazid group and fewer adverse effects (erythema: 8.6% vs. 25.7%, burning: 7.1% vs. 30.0%), reinforce this conclusion.

The study is a randomized controlled trial with an adequate sample size, enhancing the validity of the findings. It uses objective scoring (mMASI) and physician and patient assessments to evaluate comprehensive outcomes. Photographic documentation ensured visual comparison of treatment effects. However, the study was limited to a single center, which may affect generalizability. The follow-up period was relatively short, and long-term recurrence could not be assessed. Additionally, histopathological confirmation of the melasma type was not performed.

Conclusion

Topical 10% isoniazid cream demonstrated superior efficacy and fewer side effects than the standard triple combination for treating mixed

melasma. It may serve as a promising, safer alternative for long-term use. Further multicenter trials with extended follow-up are recommended.

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-CMHGUJ-093-24)
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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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