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Efficacy and Safety of Topical Metformin in the Treatment of Melasma in a Tertiary Care Hospital: A Prospective Study

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Conflict of interest: Nil

Abstract

Background: Melasma is a common acquired pigmentary disorder characterized by symmetrical hyperpigmented macules and patches, predominantly affecting females. Ultraviolet radiation, hormonal influences, genetic predisposition, and metabolic factors contribute to its pathogenesis. Metformin, a biguanide drug, has anti-inflammatory, antioxidant, and anti-melanogenic properties, making it a potential therapeutic option for melasma.

Aim and Objectives: To evaluate the efficacy, safety profile, tolerability, and clinical response of topical 15% metformin cream in the treatment of melasma.

Material and Method: A hospital-based prospective study was conducted in the Department of Dermatology, Venereology and Leprosy, Santhiram Medical College and General Hospital, Nandyal, from June 2025 to August 2025. Thirty clinically diagnosed female patients with facial melasma were included. After written informed consent and patch testing, patients were advised to apply topical 15% metformin cream twice daily for 12 weeks along with sunscreen. Modified Melasma Area and Severity Index (mMASI) scores were assessed at baseline, 4 weeks, and 12 weeks. Adverse effects were recorded during follow-up.

Result: Among 30 patients, the majority belonged to the 31-40 years age group. Centrofacial melasma was the most common pattern, seen in 18 patients (60%), followed by malar melasma in 12 patients (40%). At baseline, 11 patients (36.7%) had mild melasma, 15 patients (50%) had moderate melasma, and 4 patients (13.3%) had severe melasma. At 12 weeks, 13 patients (43.3%) had mild melasma, 11 patients (36.7%) had moderate melasma, and 2 patients (6.7%) had severe

melasma. Overall, 8 patients (26.7%) showed clinical improvement. Four patients (13.3%) discontinued treatment after 4 weeks due to burning sensation, itching, and erythema.

Conclusion: Topical 15% metformin cream appears to be an inexpensive and easily available treatment option for melasma. However, improvement within 12 weeks was modest, and larger controlled studies with longer follow-up are required to establish its efficacy and safety.

Keywords: Melasma, Metformin, Topical therapy, mMASI, Hyperpigmentation

Introduction

Melasma is a common acquired disorder of pigmentation characterized by symmetrical, irregular, light-to-dark brown macules and patches, most commonly involving the face. It is more prevalent in women of reproductive age and in individuals with darker skin types. Clinically, melasma presents in centrofacial, malar, and mandibular patterns.

The pathogenesis of melasma is multifactorial. Ultraviolet radiation, visible light, hormonal factors, genetic predisposition, pregnancy, oral contraceptive use, inflammation, and metabolic influences have all been implicated. Increased melanocyte activity, increased melanin synthesis, dermal melanophages, vascular changes, and basement membrane disruption contribute to the chronic and recurrent nature of the disease.

Treatment of melasma remains challenging because of variable response and frequent recurrence. Strict photoprotection is the cornerstone of management. Commonly used topical agents include hydroquinone, triple combination cream, azelaic acid, kojic acid, retinoids, tranexamic acid, and other depigmenting agents. Modified Kligman's formula or triple combination cream is considered one of the most effective topical therapies, but long-term use may be associated with irritation, erythema, steroid-related adverse effects, and other complications.

Metformin is a biguanide drug widely used as an oral antidiabetic agent. In addition to its glucose-lowering action, it has anti-inflammatory, antioxidant, insulin-sensitizing, and anti-melanogenic effects. Experimental studies suggest that metformin inhibits melanogenesis by reducing cyclic adenosine monophosphate signaling and downregulating microphthalmia-associated transcription factor, tyrosinase, and related melanogenic proteins. These properties support its possible role in hyperpigmentary disorders such as melasma.

Clinical studies on topical metformin in melasma are limited but encouraging. Hence, this prospective study was conducted to evaluate the efficacy and safety of topical 15% metformin cream in patients with melasma attending a tertiary care hospital.

Material and Method

This was a hospital-based prospective study conducted in the outpatient department of Dermatology, Venereology and Leprosy at Santhiram Medical College and General Hospital, Nandyal, Andhra Pradesh, from June 2025 to August 2025.

A total of 30 clinically diagnosed female patients with facial melasma were included by convenience sampling. The study was approved by Institutional Ethics Committee and written informed consent was taken from all patients.

Female patients aged 18-50 years with clinically diagnosed facial melasma who were willing to participate and attend follow-up for 12 weeks were included. Male patients, pregnant women, lactating mothers, patients who had used systemic retinoids or topical depigmenting agents in the preceding 4 weeks, patients with

uncontrolled diabetes mellitus, contraindications to metformin, hypersensitivity to any component of the formulation, and active facial skin infections or inflammatory dermatoses were excluded.

Topical 15% metformin cream was prepared by incorporating 15 g of metformin powder into 85 g of vanishing cream. The vanishing cream base consisted of stearic acid, potassium hydroxide, glycerin, methylparaben, and purified water. After pH testing, the cream was stored in an amber-colored container.

Figure 1: Equipment and materials used in the preparation of Metformin cream

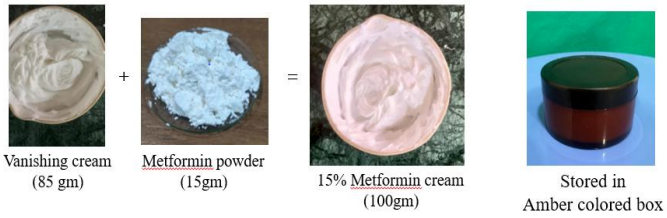
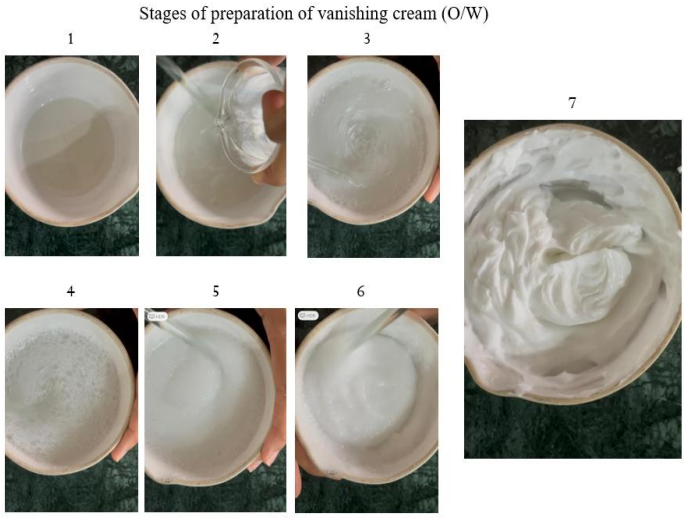


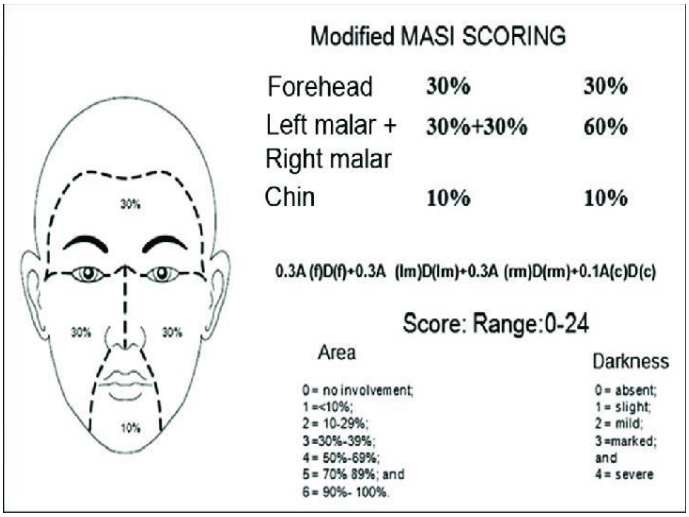
Figure 2: Stages of preparation of vanishing cream



A detailed history was recorded regarding age, duration of melasma, sun exposure, distribution pattern, color of lesions, and relevant clinical details. Clinical photographs were taken and mMASI scores were calculated at baseline. Patients were advised to apply sunscreen in the morning and afternoon. After patch testing, patients were instructed to apply topical 15% metformin cream twice daily, in the morning and at night, for 12 weeks. Follow-up assessments were done at 4 weeks and 12 weeks.

mMASI grading was interpreted as follows: 0-5 mild, >5-10 moderate, >10-15 severe, and >15 very severe.

Figure 3: Modified MASI scoring



Statistical analysis

The collected data were tabulated and analyzed using descriptive statistics. Frequencies and percentages were used to summarize demographic details, clinical characteristics, mMASI grading, treatment response, subjective assessment, objective assessment, and adverse effects.

Results: This study included 30 female patients with clinically diagnosed facial melasma.

Table 1: Age distribution of study participants

Characteristic	Number of patients	Percentage
Age 18-30 years	4	13.3%
Age 31-40 years	15	50%
Age 41-50 years	11	36.7%

Table 2: Sun exposure per day

Sun exposure	Number of patients	Percentage
Sun exposure <1 hour/day	7	23.3%
Sun exposure 1-5 hours/day	5	16.7%
Sun exposure >5 hours/day	18	60%

Table 3: Duration of melasma

Duration	Number of patients	Percentage
Duration <1 year	7	23.3%
Duration 1-5 years	12	40%
Duration >5 years	11	36.7%

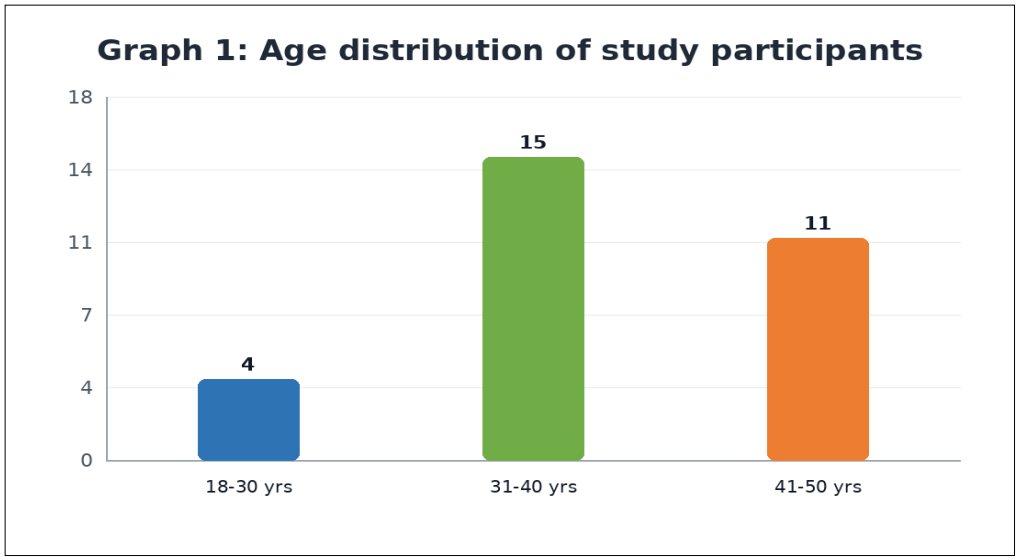
Table 4: Distribution pattern of melasma

Pattern	Number of patients	Percentage
Centrofacial pattern	18	60%
Malar pattern	12	40%
Mandibular pattern	0	0%

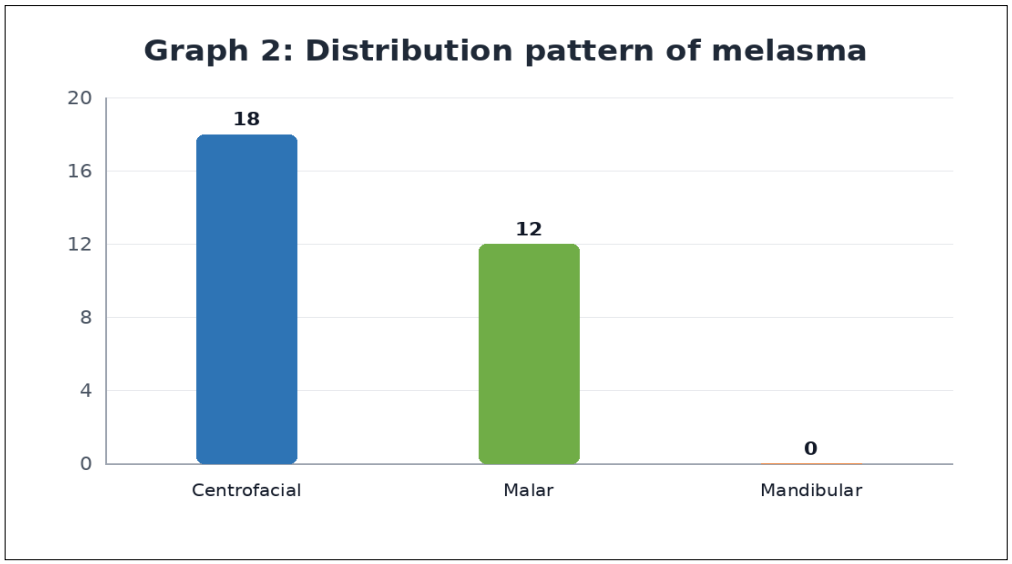
Table 5: Colour of melasma

Colour	Number of patients	Percentage
Light brown color	7	23.3%
Dark brown color	19	63.3%
Mixed color	4	13.3%

Graph 1: Age distribution of study participants



Graph 2: Distribution pattern of melasma

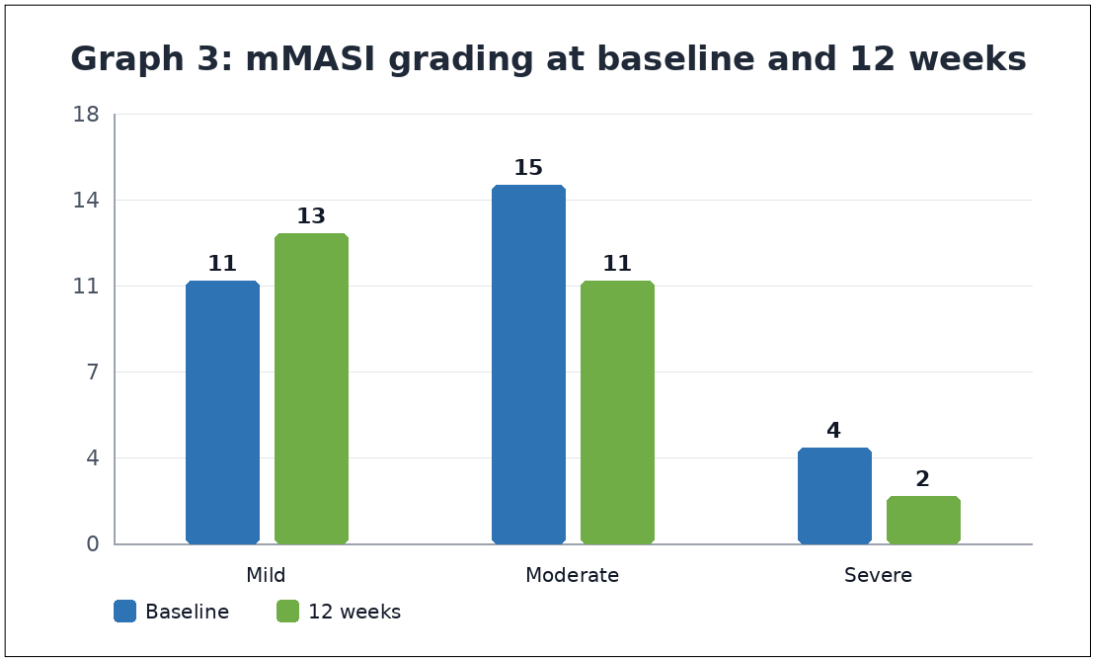


The majority of patients were in the 31-40 years age group. Most patients had daily sun exposure of more than 5 hours. Centrofacial melasma was the most common pattern, followed by malar melasma. Dark brown pigmentation was the most common clinical presentation.

Table 6: mMASI grading at baseline, 4 weeks, and 12 weeks

mMASI grade	Baseline	4 weeks	12 weeks
Mild	11	7	13
Moderate	15	15	11
Severe	4	4	2

Graph 3: mMASI grading at baseline and 12 weeks



At baseline, most patients had moderate melasma. At 12 weeks, the number of patients in the mild category increased, while moderate and severe categories decreased.

Out of 30 patients, 8 patients (26.7%) showed clinical improvement. Among these, 6 patients (20%) improved from moderate to mild mMASI grade, and 2 patients (6.7%) improved from severe to moderate mMASI grade. No significant improvement was observed in 18 patients (60%). Four patients (13.3%) discontinued treatment after 4 weeks due to adverse effects.

Graph 4: Treatment response after 12 weeks

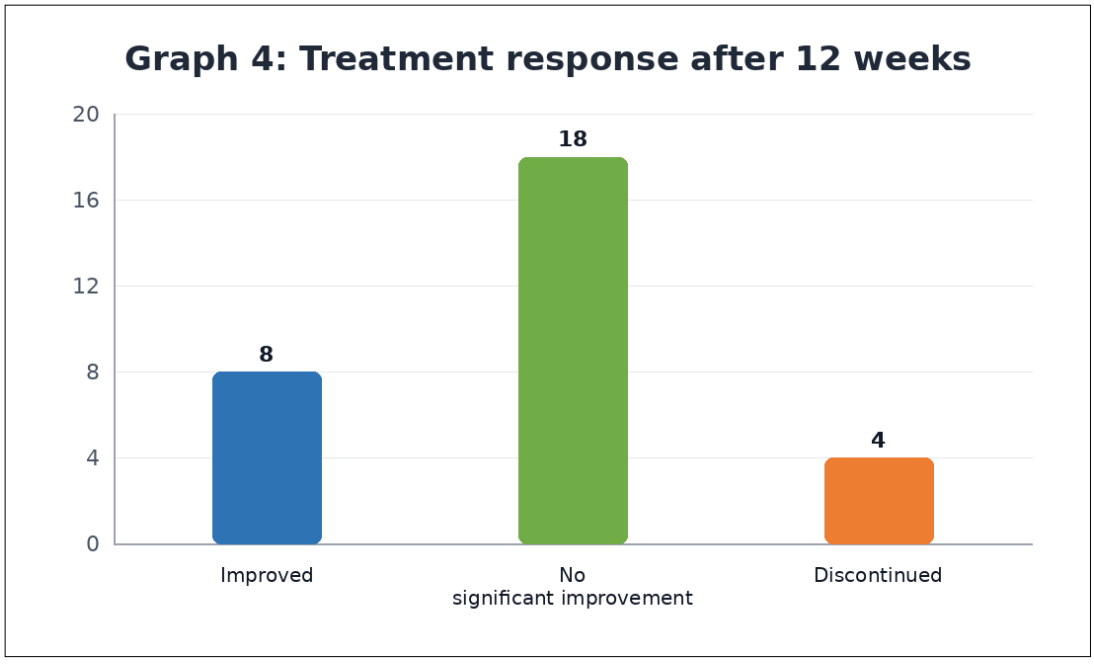


Table 7: Subjective assessment

Subjective assessment	4 weeks	12 weeks
Very dissatisfied	13	5
Dissatisfied	14	8
Somewhat satisfied	3	13
Satisfied	0	4
Very satisfied	0	0

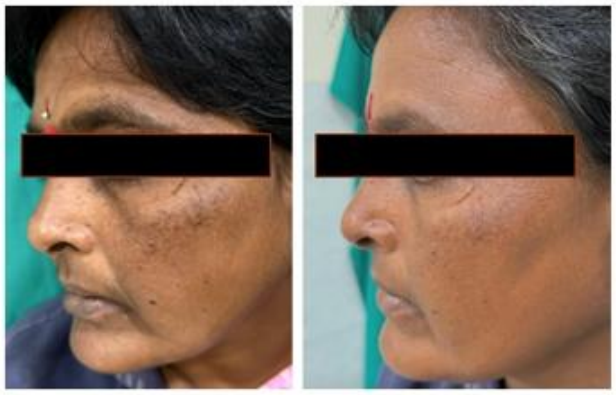
Table 8: Objective assessment

Objective assessment	4 weeks	12 weeks
Poor clearance	29	18
Moderate clearance	1	9
Good clearance	0	3
Excellent clearance	0	0

At 12 weeks, patient satisfaction improved, with 13 patients being somewhat satisfied and 4 patients being satisfied. On observer assessment, 9 patients showed moderate clearance and 3 patients showed good clearance at 12 weeks.

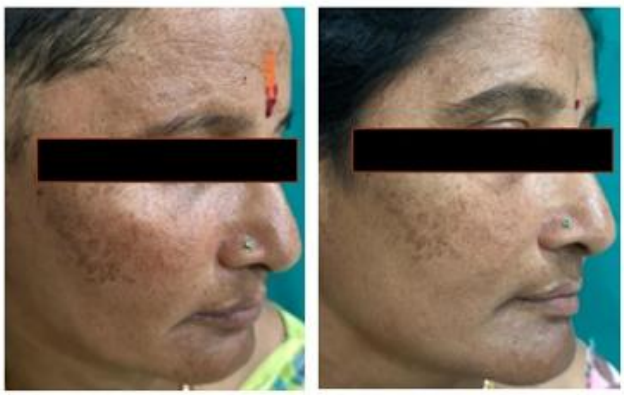
Four patients discontinued topical metformin after 4 weeks due to local adverse effects including burning sensation, itching, and erythema. No systemic adverse effects were documented.

Patient 1



BASELINE AT 12 WEEKS

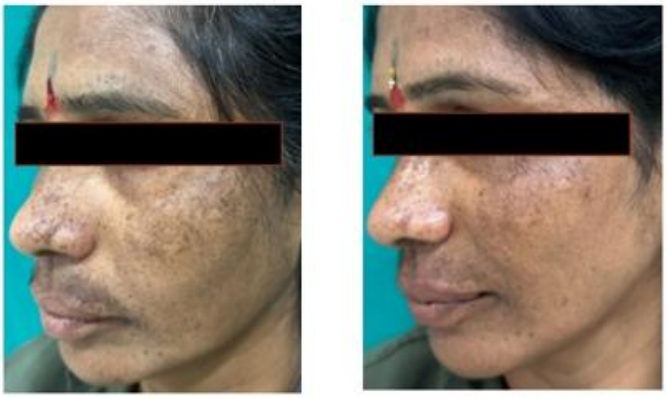
Patient 2



BASELINE AT 12 WEEKS

mMASI grade improved from moderate to mild in patients 1 and 2.

Patient 3



BASELINE AT 12 WEEKS

mMASI grade improved from severe to moderate in patient 3.

Discussion

Melasma is a chronic and recurrent acquired hyperpigmentary disorder that commonly affects women. In the present study, all patients were females aged 18-50 years, with the majority belonging to the 31-40 years age group. This is consistent with the known epidemiological pattern of melasma, which is commonly seen in women of reproductive age.

Centrofacial melasma was the most common pattern in this study, observed in 60% of patients, followed by malar melasma in 40%. Most patients had dark brown pigmentation, and a significant proportion had melasma for more than one year, indicating the chronic nature of the disease.

Sun exposure is an important aggravating factor in melasma. In this study, 60% of patients had sun exposure of more than 5 hours per day. This highlights the importance of regular photoprotection in all patients receiving treatment for melasma.

Topical metformin has gained attention as a potential depigmenting agent due to its anti-melanogenic effect. Experimental studies suggest that metformin reduces melanogenesis by decreasing cAMP accumulation and downregulating MITF, tyrosinase, and other melanogenic proteins. It also has anti-inflammatory and antioxidant effects, which may be relevant in melasma pathogenesis.

In the present study, topical 15% metformin cream applied twice daily for 12 weeks produced clinical improvement in 8 patients (26.7%). Six patients improved from moderate to mild mMASI grade and 2 patients improved from severe to moderate grade. These findings suggest that topical metformin may have a role in reducing pigmentation in a subset of patients, but the overall response was modest within the 12-week treatment period.

Mapar et al. conducted a randomized double-blind clinical trial comparing topical metformin with placebo in melasma and observed a decreasing trend in MASI scores with metformin therapy. Banavase Channakeshavaiah and Andanooru Chandrappa reported topical metformin as a novel, safe, and nearly comparable modality to triple combination cream. AboAlsoud et al. compared topical 30% metformin cream with triple combination cream and found it to be an effective and safe alternative.

A systematic review and meta-analysis by Mongkhon et al. included three randomized controlled trials involving 140 patients and reported that 15% topical metformin significantly reduced MASI score compared with placebo after 8 weeks. It also reported that 30% topical metformin showed similar efficacy to triple combination cream in reducing MASI scores after 8 weeks, although the certainty of evidence was low to very low.

Compared with these studies, the present study showed a lower proportion of clinically significant improvement. Possible reasons include small sample size, absence of a control group, use of 15% concentration rather than 30%, chronicity of melasma, high daily sun exposure, and relatively short follow-up. Melasma often requires

prolonged therapy, strict photoprotection, and maintenance treatment.

Topical metformin was tolerated by most patients, but 4 patients discontinued treatment due to burning sensation, itching, and erythema. These local adverse effects may be related to the formulation or individual skin sensitivity. No systemic adverse effects were observed.

Conclusions

Topical 15% metformin cream appears to be an inexpensive and easily available modality for the treatment of melasma. In the present study, modest clinical improvement was observed in 26.7% of patients over 12 weeks, mainly in the form of improvement from moderate to mild and severe to moderate mMASI grades. However, 60% of patients did not show significant improvement, and 13.3% discontinued treatment due to local adverse effects. Larger randomized controlled studies with longer follow-up are required to establish the efficacy, safety, optimal concentration, and ideal duration of topical metformin therapy in melasma.

Limitations

Small Sample Size: The study included only 30 patients, which limits the statistical strength of the findings. A larger sample size may provide more reliable assessment of the efficacy and safety of topical metformin in melasma.

Lack of Control Group: This was a prospective study without a placebo or standard-treatment control group. Hence, the improvement observed cannot be compared directly with spontaneous improvement, sunscreen effect, or established topical therapies.

Short Duration of Follow-up: The treatment duration was limited to 12 weeks. Melasma is a chronic and recurrent condition, and a longer follow-up period is required to assess sustained improvement, relapse, and long-term safety.

Single-Centre Study: The study was conducted in a single tertiary care hospital, which may limit the generalizability of the findings.

Subjective Components in Assessment: Although mMASI scoring was used, patient satisfaction and observer assessment may have subjective variation.

List of abbreviations

Abbreviation	Full form
DVL	Dermatology, Venereology and Leprosy
mMASI	Modified Melasma Area and Severity Index
MITF	Microphthalmia-associated transcription factor
cAMP	Cyclic adenosine monophosphate
TCC	Triple combination cream
UV	Ultraviolet
OPD	Outpatient department

KOH	Potassium hydroxide
SPF	Sun protection factor

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