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Research Article

Comparison of Topical Metformin 40% Cream with Triple Combination Cream in Treatment of Melasma in Females

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Abstract

Background: Melasma is a common acquired illness characterized by an outbreak of brown and often symmetrical hyperpigmented patches on frequently sun-exposed face areas. Its treatment is important because it affects the patient's appearance. Although topical treatments are used several times daily and for several months, they partially eliminate the lesions. This study aimed to assess and compare the efficacy of topical metformin with triple combination cream (TCC) in treating melasma.

Methods: A randomized controlled trial was carried out at the clinic of the Department of Dermatology in Imam Hassan Teaching Hospital in Karbala. Fifty females with melasma were selected. They were divided equally (25 patients) into two groups. Group A was given topical metformin 40% once daily for 2 months, and Group B was given TCC for 2 months. The patients were followed up during the treatment period.

Results: The mean age of group A was 35.06± 6.46 years, and in group B it was 34.02 ± 5.37 years. The decrease in Melasma Area and Severity Index (MASI) score was more among the metformin group (A) at 2 weeks with statically significant (p= 0.025) and a high percent of satisfaction (72%), while at 8 weeks there was no statistical difference in MASI score and the satisfaction was 88% in the metformin group.

Conclusions: Melasma can be treated safely and novelly with topical metformin, which is as effective as TCC.

Keywords: metformin, melasma, triple combination

Introduction

Melasma is a common, acquired, circumscribed hypermelanosis of the face and occasionally of the neck and forearms, which significantly impacts the quality of life. Although it may affect any race, melasma is much more common in darker-skinned individuals (skin types IV to VI) [1]. Etiopathogenesis of melasma is multifactorial and remains unclear. Genetic and hormonal factors and exposure to UV radiation are classical influencing factors. Many other factors may play a role in the etiology of melasma, such as ingredients in cosmetics, phototoxic and anti-seizure drugs, and endocrine disorders [2].

Metformin is an antidiabetic drug known to exert biological effects by inhibiting the energy-sensitive AMP-activated protein kinase (AMPK), a mammalian target of rapamycin [3]. Recently, metformin was shown to decrease intracellular levels of cyclic adenosine monophosphate (cAMP). Because cAMP is a well-known modulator of melanin synthesis (melanogenesis), metformin has been investigated to modulate melanogenesis. When melanocytes were treated with metformin, basal levels of total melanin were reduced significantly [4]. In addition, metformin blocked foreskolin and a-melanocyte-stimulating hormone (α-MSH)-induced increases in the levels of melanin. In order to elucidate the mechanisms by which metformin inhibits melanogenesis, the effects of metformin on the levels of three key melanogenic proteins, tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2) were examined using immunoblot analyses [5].

There are two types of melanin: dark, brown-black eumelanin and red-yellow sulfur-containing

pheomelanin. Synthesis of both types of melanin involves a rate-limiting catalytic step in which the amino acid tyrosine is oxidized by tyrosinase to L-DOPA. Inhibiting this reaction is thought to block melanin synthesis, making it the critical rate-limiting step in melanogenesis. The L-DOPA is then oxidized into DOPA quinone and converted to 5,6-dihydroxyindole or 5,6-dihydroxyindole-2- carboxylic acid by TRP-2. The role of TRP-1 in human melanogenesis is not well characterized, but genetic mutations in TRP-1 in humans result in hypopigmentation, suggesting that TRP-1 has a key role in melanin synthesis [6].

Consistent with the effects of metformin on total levels of melanin, metformin decreased the basal levels of tyrosinase, TRP-1, and TRP-2, with blocked foreskolin making melanocyte stimulation hormone (MSH)-induced increases in these three key melanogenic proteins [6]. Metformin downregulates the expression of microphthalmia-associated transcription factor (MITF) through a cAMP-dependent pathway, The MITF, a basic–helix-loop-helix, and leucine zipper transcription factor, has been termed the ‘‘master gene’’ for melanocyte survival, and it is a key factor regulating transcription of the major melanogenic proteins (e.g. tyrosinase, TRP-1, TRP-2, protein kinase C-b (PKCb), and melanoma antigen recognized by T cells 1 (MART-1) [6]. Moreover, it is well documented that the expression of the MITF is upregulated by a cAMP-dependent pathway. When a-MSH binds to its melanocortin 1 receptor, intracellular levels of cAMP are elevated through the activation of the membrane-associated adenylate cyclase enzyme. The cAMP-dependent protein kinase enzyme is then activated, and it translocates to the nucleus and phosphorylates the cAMP-responsive element-binding protein (CREB) [5]. CREB then binds its DNA consensus sequence CRE in the promoter region of the MITF gene, thereby inducing MITF transcription. Using this knowledge, factors can be taken into consideration such as treated melanocytes with metformin and examining its effects on the intracellular levels of cAMP, activation of protein kinase A, and phosphorylation of CREB, as well as on the levels of MITF [5]. Their results showed that metformin reduced basal levels inhibited foreskolin and increased induction of the α-MSH in the activities of protein kinase A and CREB phosphorylation, as well as increased cAMP accumulation and the levels of MITF. Thus, the studies concluded that metformin inhibits melanogenesis by downregulating the expression of MITF through a cAMP-dependent pathway [7].

Although the AMPK (AMP-activated protein kinase) pathway has not been implicated in regulating melanogenesis, it has been well-documented that AMPK is one of the major mediators of metformin’s biological effects. Thus, Lehraiki *et al.* (2014) examined the possible role of AMPK in inhibiting melanogenesis by metformin [5]. Melanocytes were transfected with control or dominant-negative AMPK, and control siRNA, or siRNA against AMPK. Interestingly, neither dominant-negative AMPK nor siRNA against AMPK blocked the inhibitory effects of metformin on melanogenesis. These results demonstrated that AMPK is not involved in mediating the inhibitory effects of metformin on melanogenesis [6].

Studies have shown that Wnt/b-catenin also has an important role in the expression of MITF. Treatment of melanocytes with metformin resulted in the downregulation of phosphorylated b-catenin in both basal and foreskolin-stimulated conditions. Otherwise, metformin has no effect on the transcriptional activity of b-catenin induced by foreskolin, suggesting that the Wnt/b-catenin pathway is not involved in mediating the inhibitory effects of metformin on melanogenesis. Both protein kinase c (PKC) and cAMP-dependent pathways were implicated in the crosstalk that regulates melanogenesis [7]. Endothelin-1 and histamine were also shown to utilize both PKC and cAMP-dependent pathways to exert their regulatory effects on melanocyte function. Therefore, it is possible that metformin utilizes both PKC and cAMP-dependent pathways to exert its biological actions. Indeed, it was shown that metformin could inhibit the activation of PKC-b and PKC-b which has been well-documented to regulate melanogenesis [8].

The PKC is a serine/threonine kinase C which is activated by diacylglycerol, a component cleaved from the plasma membrane when cell surface receptors interact with their ligands. Diacylglycerol induces PKC translocation to membranes, where the latter is activated to induce phosphorylation of serine/threonine residues on target proteins such as tyrosinase [7]. The PKC-b isoform is specifically involved in regulating tyrosinase activity. It interacts with receptor-activated C-kinase when activated by diacylglycerol and then anchors onto melanosomes, the organelle where melanogenesis occurs, and phosphorylates tyrosinase (phosphorylation activates tyrosinase) [8]. Therefore, the decrease in pigmentation caused by metformin as observed by Lehraiki *et al.* (2014) may also involve the inhibition of tyrosinase activity through the inhibition and activation of PKC-b [5]. The MITF has also been shown to regulate the expression of PKC-

b, suggesting that metformin may utilize both cAMP and PKC-dependent pathways to downregulate melanin synthesis [9].

Metformin decreased skin pigmentation *in vivo* with minimal side effects, suggesting a potential application of metformin in the treatment of hyperpigmentation disorders. Where the metformin was applied topically onto a mouse tail, whitening of the tail was observed. In addition, metformin decreased the epidermal level of melanin when metformin was applied to human skin punch biopsies and reconstructed human epidermis [9]. Therefore, this study was designed to evaluate the safety and efficacy of topical metformin in the treatment of melasma and to compare its efficacy with the TCC (hydroquinone 4% + tretinoin 0.05% + fluocinolone acetonide 0.01%).

Materials and Methods

Study design

A randomized controlled trial study to compare the treatment of melasma by topical metformin lotion 40% with treatment by a triple combination (TCC) of hydroquinone 4%, tretinoin 0.05%, and flucinolone acetonid 0.01%.

Patients

A total of 50 patients with melasma were conducted at Imam Hassan Teaching Hospital, which is one of five hospitals of the Karbala Health Directorate in Karbala governorate. Every hospital has a dermatology department which is distributed according to the geographical location and population divisions. The Karbala governorate is 5,043 square kilometers. The clinical study was carried out for six months from October 2019 to the end of March 2020. Patients were selected by non-random sampling method according to specific criteria that were included in the study as a convenience sample and divided into two groups. Group A included 25 patients with melasma who were diagnosed by the consultant dermatologists in the dermatology department of the hospital and treated with topical metformin lotion 40%. Group B included 25 patients with melasma who were treated by the TCC. The hospital was visited by patients 5 times a week and 4 hours per day. Patients were followed for detailed history, cutaneous examination, and clinical diagnosis of melasma.

Inclusion and exclusion patients

Volunteers who were over 18 years old and had melasma without topical or systematic treatment for 6 months were part of this study. Patients who had no treatment with laser, or surgical treatment on their faces during the previous year were also included.

Excluded patients included those not willing to participate, pregnant women and lactating mothers, and those treated with oral contraceptive pills, antiandrogen, systemic metformin, or oral retinoids within 6 months before the study. Other excluded patients were those with systematic disease (stomach, liver, pancreas disease), diabetes, a history of hypersensitivity to some of the components of the formulas of the study, and coexistence of associate diseases and other pigmentation diseases. Patients with poor wound healing, recurrent herpes labialis, and current skin infection (facial warts, molluscum contagiosum, history of hypertrophic scar/keloids, active dermatosis of atopic, seborrheic or other eczematous type), photosensitivity, and occupation involving primarily outdoor activities were also excluded.

Data Collection Tool

A structured questionnaire was used for data collection. It consisted of demographic information including full history from each patient (age, gender, occupation, sun exposure, residence, and marital state), maternal information (pregnancy, history of contraceptive and breastfeeding), disease information (duration, skin types, hormone therapy, previous treatment, history of DM, endocrine disorder, MASI score, and patient satisfaction), and a history of close physical examination which was done by dermatologists to evaluate the severity of melasma.

Drug preparation

Metformin lotion was prepared by mixing 40 gm of metformin powder (Metformin Awa, manufactured by Iraq) with 70% alcohol and propylene glycol 30% (w/v). This preparation resembles 40% metformin lotion which was dispensed as 50 ml to patient group A. Hydroquinone 4%, tretinoin 0.05%, and flucinolone acetonid 0.01% as a triple combination (triderm. Derma Pella Pharmaceuticals™, Jordan) were used for group B.

Pigmentation was assessed using the Melasma Area and Severity Index (MASI) score at baseline after 2 weeks to 8 weeks. The MASI score is calculated by subjective assessment of 3 factors: area of involvement (A), darkness (D), and homogeneity (H), with the forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of the total face, respectively. The involvement of each of these 4 areas is given a numeric value of 0 to 6 (0: no involvement, 1: 10%, 2: 10%-29%, 3: 30%-49%, 4: 50%-69%, 5: 70%-89%, and 6: 90%-100%). Darkness and homogeneity are rated on a scale from 0 to 4 (0: absent, 1: slight, 2: mild, 3:

marked, and 4: maximum). The MASI score is calculated by adding the sum of the severity ratings for darkness and homogeneity, multiplied by the value of the area of involvement, for each of the 4 facial areas [10].

MASI score = 0.3 A(f) [D+H] + 0.3 A(lm) [D+H] + 0.3 A (rm) [D+H]+ 0.1 A (c) [D+H].

Outcome measures included a global improvement scale (grades 0-4) and patient satisfaction. Group A was advised to apply a thin film of metformin 40% lotion over the affected area on the face at night after shaking the bottle well. Similarly, patients in group B who were treated with TCC were advised to apply a thin film cream over the affected area on the face at night. Patients in both groups were followed up once in 2 weeks to assess the improvement and to look for any adverse effects. The MASI score was calculated at each visit, and the percentage of improvement was calculated by deducting the MASI score from the pretreatment MASI score and dividing it by the pretreatment MASI score in 8 weeks of treatment [10].

Grading score according to global improvement scale as:

Grade 0: no improvement.

Grade 1: mild improvement (1 to < 25%).

Grade 2: moderate improvement (25 - 50%)

Grade 3: marked improvement (50- 75%)

Grade 4: nearly total or total improvement (> 75%).

Any adverse effect was noted and treated accordingly. Subjected assessment was done by patients based on their level of satisfaction with treatment and was scored on a scale of 0-4 (0: no, 1: poor, 2: slightly, 3: satisfied, and 4: highly satisfied) [10].

Ethical approval

This study was approved by the ethical committee of the Karbala Directorate of Health of the Iraqi Ministry of Health in No.2025180 on 8 January 2020. The collected data was kept confidential and not be divulged except for the purpose of the study. The patient concerts were taken when all voluntarily participated and they have the right to withdraw from the study.

Statistical Analysis

Data was translated into a computerized database structure. Statistical analyses were done using SPSS (Statistical Package for Social Sciences) version 20 computer software for Windows. Categorical variables were presented as frequency and percentage. The Chi-square and t-test were used to test the significance of the association between categorical variables with a considered p-value of ≤ 0.05 was statistically significant.

Results

The fifty patients with melasma were distributed equally between the two groups and without any statistically significant association (p=1.00). The patient's age ranged from 28 to 41 years (mean, 34.5 years). The mean age was separately 35.06± 6.46 in group A and 34.02 ± 5.37 in group B with no statistical significance (p = 0.614). Regarding marital state, the result showed that 84% were married and 16% were unmarried distributed between 72% married and 28% unmarried in group A, while married were more prevalent in group B (96%) with a statistically significant (p=0.049). Non-employed patients (78%) were more frequent and distributed between the two groups, 42% in group A and 36% in group B without any statistical difference (p=0.439) (Table 1)(Figure 1).

Table 1: Distribution of patients according to sociodemographic characteristic

		Groups		Total No.
		Group A	**Group B**	
SEX	Females	24	24	50
Total No.		25	25	50
Fisher's Exact Test = 0.00		df= 1	p-value= 1.00	
Age	Mean	35.06	34.02	25
	SD	6.460	5.370	25
Independent T test = 0.508		df= 48	p-value = 0.614	
		Groups		**Total**
		Group A	**Group B**	
Maritalstate	Married	18	24	42
	Unmarried	7	1	8
Total No.		25	25	50
Fisher's Exact Test = 5.037		df = 1	p-value = 0.049*	
		Groups		**Total**
		Group A	**Group B**	
Occupation	Employer	4	7	11
	Non-employer	21	18	39
Total No.		25	25	50
Fisher's Exact Test = 1.094	df= 1	p-value = 0.439		

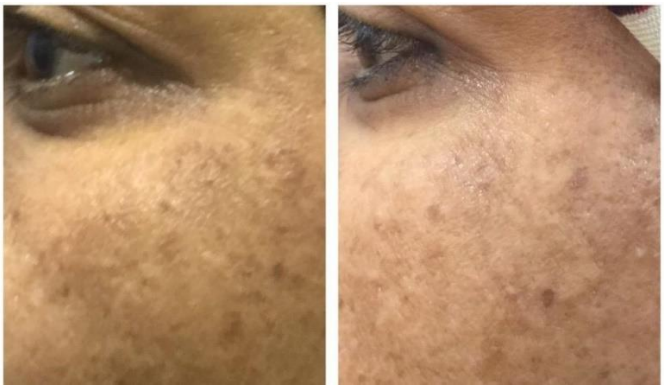

Figure 1: Treatment with topical metformin. A: Before treatment, B: After 2 weeks of treatment.

Regarding skin types, the result of the study showed that type III (84%) and type IV (16%) were more prevalent without any statistically significant association (p=0.440) (Table 2) (Figure 2). The MASI mean was higher among group B than group A (11.84 and 10.31, respectively) in zero week, but without any statistical difference. While, after 2 weeks MASI decreased more among group A than group B (MASI mean, 7.68 and 9.69 respectively) with statically significant association (p= 0.025). This association became none significant after 8 weeks (Table 3) (Figure 3). After 8 weeks of treatment, it was found that 3(12%) in group A had a mild improvement, 19 (76%) were moderate, and 3(12%) had marked global improvement scores. Group B didn't show any marked improvement with only 4(16%) mild and 21(84%) moderates without any statically significant association (p=0.198) (Table 4) (Figure 4).

Table 2: Distribution of patients according to skin types (n=50).

		Groups		Total No.
		Group A	**Group B**	
Skin types	III	20	22	42
	IV	5	3	8
Total No.		25	25	50
Fisher's Exact Test= 0.595 df= 1 p-value = 0.440				

Table 3: Comparison of patients according to MASI score.

MASI mean	No.	Group A	Group B	P-value
0 week (mean + SD)	50	10.31+ (3.66)	11.84 + (3.70)	NS
2 week (mean + SD)	50	7.68 + (2.89)	9. 69 + (3.26)	**0.025***
8 week (mean + SD)	50	6.13 + (2.31)	7.57 + (2.85)	NS
Independent T test , significant * , non-significant (NS)				

Table 4: comparison of study sample according to global improvement score

		Group A	Group B	Total No.
Global improvement score	Mild	3 (12%)	4 (16%)	7
	Moderate	19 (76%)	21(84%)	40
	Marked	3 (12%)	0	3
Total		25	25	50
Pearson Chi-Square 3.243a df=2 p-value =0.198				

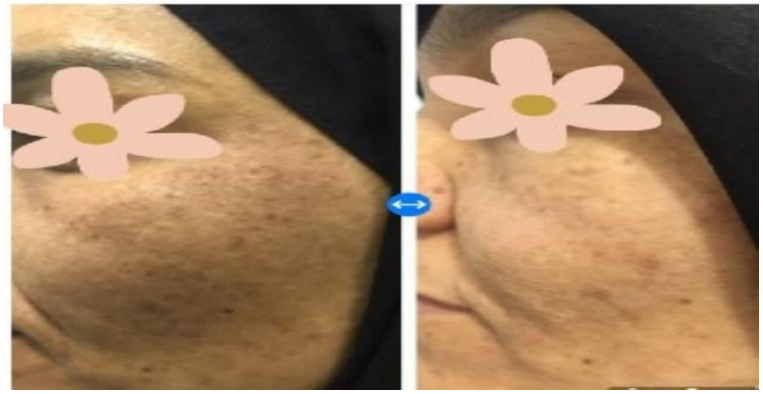

Figure 2: Treatment with topical metformin. A: Before treatment, B: After 8 weeks of treatment.

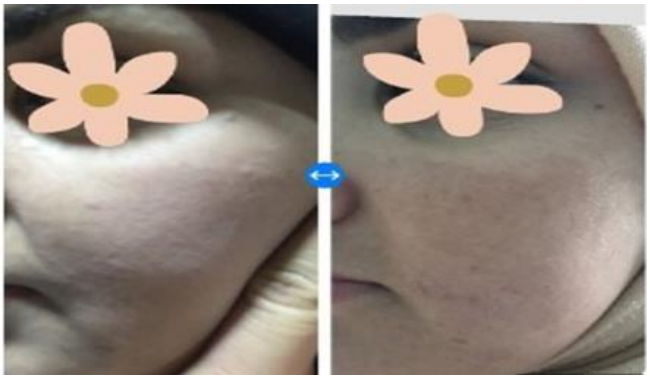

Figure 3: Treatment with topical metformin. A: Before treatment, B: After 8 weeks of treatment.

Figure 4: Treatment with topical metformin. A: Before treatment, B: After 8 weeks of treatment

Regarding the satisfaction of patients after 2 weeks, the result showed a high percent of satisfaction among patients in group A (72%) with 24% highly satisfied and 4% slightly satisfied. Patients in group B (92%) showed poor satisfaction and 8% were less satisfied with a statistically significant (p=0.000). After 8 weeks of treatment, the satisfaction assessment was 8% highly satisfied, and 88% satisfied among patients in group A, while in group B there were 92% of patients had poor satisfaction and 8% slightly satisfied with statically significant association (p= 0.00) (Table 5).

Table 5: Distribution of patients according to satisfaction scale.

		Groups		Total No.
		Group A	**Group B**	
Satsfication 2weeks	Highly satisfied	6 (24%)	0 (0%)	6
	Poor	0 (0%)	23 (92%)	23
	Satisfied	18 (72%)	0 (0%)	18
	Slightly satisfied	1 (4%)	2 (8%)	3
Total No.		25 (100%)	25 (100)	50
Pearson Chi-Square = 47.333a df= 3 p-value = 0.000*				
		Groups		**Total No.**
		Group A	**Group B**	
Satisfaction 8 weeks	Highly satisfied	2 (8%)	0	2
	Poor	0	23(92%)	23
	Satisfied	22(88%)	0	22
	Slightly satisfied	1(4%)	2 (8%)	3
Total No.		25	25	50
Pearson Chi-Square= 48.567a df= 3 p-value = 0 .000*				

Discussion

Melasma is a widespread acquired disease, which takes the form of light brown to darker areas after being exposed to sunlight. Patients with such disease suffer from a great deal of emotional pain and the occurrence of mental disorders that affect the person's health and quality of life negatively [11]. Although melasma is asymptomatic, it is a disfiguring disease that has a negative impact on the quality of life and self-esteem of those suffering from it [12].

This study is concerned with the safety and efficacy of topical metformin for the treatment of melasma. The results showed that using 40% topical metformin significantly decreased the MASI score of the study group with minimal side effects in comparison with the control group using TCC after 8 weeks. The MASI score which is used in this study uses a similar formula for the face as it is used for the whole body in the Psoriasis Area and Severity Index (PASI) score. Moreover, the three variables of MASI are the most widely used outcome measure in clinical studies on melasma. MASI score, proposed by Kimbrough-Green *et al.* in 1994 [13], has been devised on the pattern of PASI. Interestingly, the MASI uses an almost similar formula for the face as area and induration. The scaling in PASI is replaced by area, pigmentation, and homogeneity in MASI score. While the variables of pigmentation and area of involvement are certainly important to consider in melasma. [14].

Because of its strong whitening properties, TCC is regarded as the gold standard among topical treatments for melasma. The synergistic effect of its constituent parts is linked to its effectiveness [15]. However, erythema, burning, and irritation are common side effects [16]. The same side effects were also observed in this study. Recently, it has been indicated that metformin can reduce intracellular cAMP. Since cAMP plays a role in melanogenesis, metformin seems to result in the inhibition of melanogenesis [17]. Metformin results in a considerable decline in the melanin content in the basal layer. On the other hand, it plays a role in decreasing the tyrosinase enzyme levels, TRP-1 and TRP-2 which are the key proteins in melanogenesis. In addition, the decline in MITF expression via the cAMP-dependent pathway has been introduced as the other reason for melanogenesis inhibition by metformin [18]. These effects of metformin have only been observed in its topical use and have not been seen in the systemic use of the drug. The effect of metformin has been studied so far on the treatment of skin hyperpigmentation only in animal models [19].

In the current study, the result showed that the MASI mean was more among group B than group A in zero weeks and without any statically difference. Meanwhile, the MASI was high decreased after 2 weeks, among group A than group B with statically significant association. But after 8 weeks, there was no statistical difference. In a study conducted by Mapar *et al.* (2019) [20] No significant difference was observed between the two groups at the start of the study. Compared to the beginning of the study, the MASI scores were significantly decreased in both groups of placebo and metformin one month after the end of the study.

TCC was determined to be the most effective topical medication for melasma based on a prior meta-analysis assessing the effectiveness of 14 melasma treatments [21]. Furthermore, a meta-analysis that examined the effectiveness of topical treatments for melasma by comparing the MASI scores before and after therapy came to the conclusion that non-hydroquinone agents might be taken into consideration as substitutes for those that include hydroquinone [22]. To achieve significant results, the drug must be prescribed for more time. Albeit, the dosage of the drug is another possible variable. However, this hypothesis cannot be investigated due to the absence of another group with a different dosage and this may be a recommendation for future studies

Benefits of Topical Metformin in this Study include that the systemic absorption and related negative effects are minimized by topical preparations of metformin, in contrast to oral forms. Furthermore, good tolerability as research shows that it causes less skin irritation than more traditional medications like TCC [23]. Also, the adequacy for long-term use as Topical metformin exhibits potential for sustained treatment with negligible side effects [24].

Limitations of study

Limitations to this study include the Limited evidence as pilot trials and small-scale investigations are the only available data. Safety and efficacy need to be confirmed by more research. In addition to that, collecting samples has some difficulties in applying inclusion and exclusion criteria, for example, many patients were already using topical medications prescribed by outpatient clinics leading to the sample size being small. Additional investigations should incorporate a longer treatment duration and a randomized study design.

Conclusions

Topical metformin is a safe and effective treatment for moderate to severe melasma, according to the study's findings, and it works just as well as triple combination cream (TCC). In comparison to TCC, there was a significant improvement in MASI ratings as early as two weeks, along with fewer side effects and greater patient satisfaction. Given these results and its good safety record, we advise considering topical metformin as a first-line therapy option for melasma. Future research ought to examine metformin's long-term effectiveness, as it may prolong treatment over eight weeks. Further advantages could be obtained by looking at the formulation of metformin as a cream as opposed to a lotion. Finally, to maximize therapeutic results, combination therapy of topical metformin with additional modalities could be investigated.

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Author contribution: Conceptualization: A.A.S., R.M.M., Methodology: A.A.S., Formal analysis and investigation: A.A.S., R.M.M., Writing: A.A.S., Resource: A.A.S.

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