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Original Article

Comparison of effectiveness and safety of topical 30% metformin versus 4% hydroquinone in the treatment of epidermal melasma

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Abstract

Objective To compare the effectiveness and safety of topical 30% metformin versus 4% hydroquinone in the treatment of epidermal melasma.

Methods The study was a randomized controlled trial conducted at Outpatient Department of Dermatology Unit II, Mayo Hospital Lahore over a duration of six months. A total of 62 patients were enrolled from the outpatient Dermatology department as per inclusion and exclusion criteria. Two equal groups were formed randomly by lottery system, as group A and group B. In Group-A patients were advised to apply 30% Metformin cream over the affected area on the face at night and sunscreen of SPF 30 in the morning for a period of 12 weeks and in Group-B patients were advised to apply 4% Hydroquinone cream over the affected area on the face at night and sunscreen of SPF 30 in the morning for 12 weeks. Patients were asked to come for follow-up every 4 weeks till completion of the treatment (till 12 weeks) and last follow up was done one month after the last treatment session (at 16th week). All patients' photographs were taken before and after starting the therapy. MASI score for all patients was calculated at each visit. Percentage of improvement was calculated by deducting MASI score from pretreatment MASI score and dividing it by post-treatment MASI score.

Results Mean age of patients in Group-A and B was 41.29±13.01 years and 36.16±11.46 years. Among these patients 16 (25.81%) were male and 46 (74.19%) were female. The male to female ratio was 2:6. Mean percentage reduction in MASI score in Group-A and B was 60.28±14.04 and 55.02±13.35, respectively. As per efficacy criteria patients treated with metformin had higher efficacy as compared to patients treated with hydroquinone. i.e. Group-A: 80.6% vs. Group-B: 58.1%, p-value=0.054. No significant difference was seen for hypopigmentation and swelling between both groups from 1st month till 4th month follow up post treatment.

Conclusion The present study showed that 30% topical metformin is more effective and safe as compared to 4% hydroquinone in the treatment of epidermal melasma.

Key words
Epidermal; Melasma; Metformin; Hydroquinone.

Introduction

Melasma is characterized by hyper-melanosis of sun-exposed skin regions and is a pigmentary condition that has developed over time. This condition, which is often referred to as the "mask of pregnancy", disproportionately affects pregnant women and has consistently been shown to be more common in females.[1] Exposure to UV radiation is associated with an elevated risk of skin cancer in some ethnic groups, including those of East Asian, Indian,

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Pakistani, Middle Eastern, Mediterranean-African, and Hispanic descent, according to epidemiological research.[2] There is some evidence that heredity plays a role in the development of melasma; in fact, it has been shown to run in families at a rate of 61%.[3]

A variety of methods are currently employed to assess pigmentary disorders and their severity. These methods include reflectance spectroscopy, computer-assisted area measurements, the Melasma Severity Scale, the Melasma Area and Severity Index (MASI) score, the Physician's Global Assessment (PGA) score, and the Investigator's Global Assessment (IGA).[4] In cases where refractory or mixed kinds of melasma are present, treatment might be challenging.

Melasma therapies may be administered topically, orally, surgically, or in conjunction with other methods. Photodamage, inflammation, vascularity, and pigmentation are all targets of these approaches to melasma etiology.[5] Most of the common methods for treating melasma, such as chemical peels, lasers, steroids, azelaic acid, and topical hydroquinone (HQ), fail to provide consistently good results.[6,7]

The use of hydroquinone (HQ) is supported by substantial evidence, and it is regarded as the first-line of therapy for melasma. HQ, which inhibits the tyrosinase enzyme in melanin synthesis, is chemically known as 1,4-dihydroxybenzene. Several randomized controlled trials have compared different treatment regimens using 4% hydroquinone. Both the efficacy and safety profiles of hydroquinone were found to be equivalent in these studies.[8-10]

Therefore, the search for the perfect therapy that effectively reduces melasma pigmentation while leaving no side effects has persisted. The use of metformin to treat melasma has been mentioned in a few recent papers.[11,12] Metformin may have a place in the treatment of hyperpigmentation disorders due to its ability to reduce skin pigmentation in-vivo with few adverse effects.[13] A number of melanogenic proteins, including tyrosinase, TRP 1, TRP 2, and protein kinase C beta, are downregulated in response to topical metformin, according to recent in-vitro investigations. This is brought about by a decrease in the expression of MITF.[14,15] Metformin cream, according to Iranian researcher Mohammad Ali Mapar, dramatically lowers patients' MASI scores without influencing their test indicators.[11]

Topical metformin has recently emerged as a treatment modality for treating melasma patients due to its melanopenic effects. Studies have reported good efficacy and minimal side effects for topical metformin. Additionally no local study has tested its efficacy and safety in our local population. Keeping in mind the depigmenting potential, cost effectiveness and its availability makes it a potential modality to be tested in comparison to other standard treatment modalities in our local settings for treating melasma patients. Therefore, it is imperative to conduct this study to see if topical metformin is equally/ more effective than hydroquinone treatment. It can then be recommended in routine clinical practice for treating melasma patients.

Methods

The present study was a randomized controlled trial (RCT), conducted at the Department of Dermatology, KEMU/ Mayo Hospital, Lahore. Hospital Ethical review board committee gave the approval for this study. A total of 62 patients aged 18-50 years either gender presenting with epidermal melasma of any duration diagnosed under wood’s lamp examination, Fitzpatrick skin types (FST) IV-V were included in the study.

Patients with HIV, hepatitis B&C infection, diabetes mellitus, bleeding disorders, herpes simplex infection (based on medical examination and history), pregnant and breastfeeding women, patients with acne, rosacea, or other active skin diseases on the face were excluded from the study. This study excluded patients who were using metformin, carbamazepine, phenytoin, spironolactone, tetracycline, or oral contraceptives. Individuals who had recently had oral and systemic melasma therapy were also not included.

All patients had given written informed consent. Using the lottery method, patients were allocated into two groups, A and B, each with 31 patients. Convenience sampling with non-probability was used to choose the patients. In Group-A patients were advised to apply 30% Metformin cream over the affected area on the face at night and sunscreen of SPF 30 in the morning for a period of 12 weeks. In Group-B patients were advised to apply 4% Hydroquinone cream over the affected area on the face at night and sunscreen of SPF 30 in the morning for 12 weeks. Patients were asked to come for follow-up every 4 weeks till completion of the treatment and last follow up was done one month after the last treatment session (at 16th week). Patients' pre- and post-treatment photographs were taken, and each visit's MASI score was computed. The percentage of improvement will be determined by subtracting the MASI score from the pre-treatment MASI score and dividing the result by the pretreatment MASI score. During the course of the therapy, any adverse effects were noted and dealt with in accordance with usual procedure. SPSS version 23 was used for data entry and analysis. Quantitative variables like age, duration, pre-and post-treatment MASI score were measured in the form of mean±SD. Qualitative variables like gender and site were presented using frequency and percentage. Effectiveness of treatment between groups was compared with independent sample t-test. However, effectiveness of treatment within group before and after treatment was assessed with the help of paired sample t-test. Chi square test was applied to compare safety of treatment between groups. p-value <0.05 was considered statistically significant.

Results

Mean age of patients in Group-A and B was 41.29±13.01 years and 36.16±11.46 years, respectively. Mean duration of melasma for patients in Group-A and B was 20.87±11.64 months and 19.23±12.15 months, respectively. 16 patients (25.81%) were male and 46 (74.19%) were female. The male to female ratio was 2:6. In Group-A 10 (32.26%) patients were

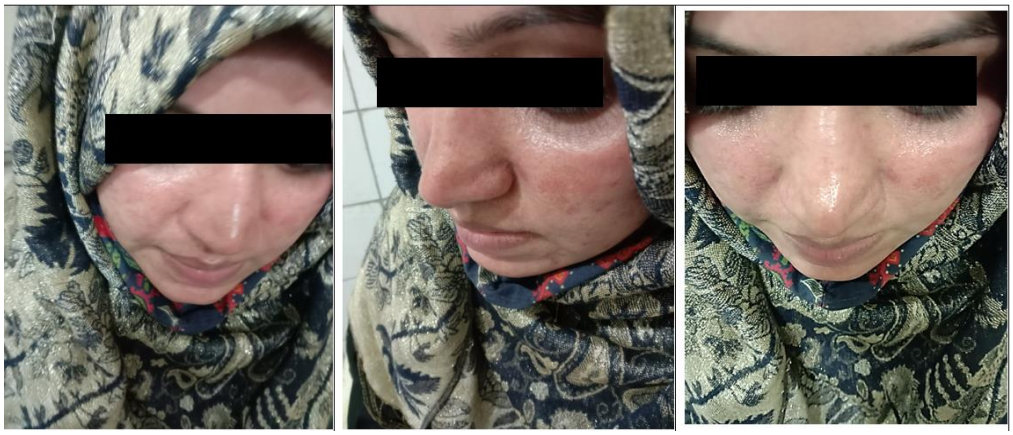

Figure1 Epidermal Melasma in a patient treated with topical metformin followed over 3 months time.

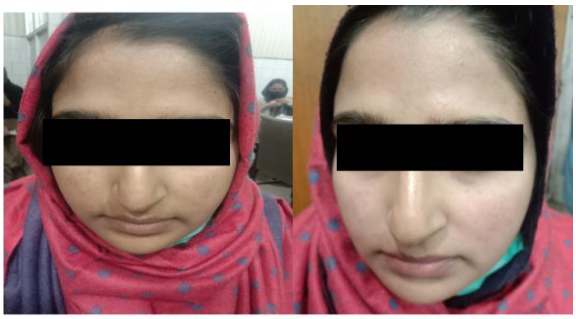

Figure 2 Epidermal Melasma in a patient at 1st and 4th month of treatment with topical metformin.

Table 1 Percent reduction of MASI score in study groups.

	Group-A	*Group-B*
Before Treatment	14.84±3.56	14.45±3.18
1st Month	13.48±3.54	13.13±3.03
2nd Month	12.06±3.59	11.55±3.13
3rd Month	10.61±3.61	10.03±3.07
4th Month	5.94±2.77	6.42±2.32
Percent reduction in MASI Score	60.28±14.04	55.02±13.35

Table 2 Efficacy in treatment group.

	Group-A (Metformin)	*Group-B (Hydroquinone)*	*Total*
Yes	25 (80.6%)	18 (58.1%)	43
No	6 (19.4%)	13 (41.9%)	19
Total	31	31	62
p-value 0.054			

male and 21 (67.74%) were female while in Group-B 6 (19.35%) were male and 25 (80.65%)were female. In Group-A 7 (22.58%) patients and in Group-B 9 (29.03%) patients had a family history of Melasma. There were male and female with Melasma having ratio.

Regarding the pattern of melasma, the most frequent type among patients was malar followed by mandibular and centro facial.

As per efficacy criteria patients treated with metformin had higher efficacy as compared to patients treated with hydroquinone i.e. Group-A: 80.6% vs. Group-B: 58.1%, p-value=0.054 (**Table 2)**.

Erythema, irritation and swelling were noted in both groups in 2-3 patients in each group which was transient and settled down with the passage of time.

Discussion

We live in a world where melasma is a frequent skin condition. Hydroquinone, kojic acid, azelaic acid, arbutin, ascorbic acid, chemical peels, lasers, tranexamic acid, and several plant extracts are among the many treatment techniques that have been attempted to treat melasma, with varying degrees of success.[7] The combination of these creams is still beneficial, but it comes with major side effects when used for an extended period of time.[16,17] Topical metformin was recently studied for its melanopenic effects and potential use in melasma. Hydroquinone (HQ) is the most popular and most widely studied medication in the management of melasma.

In present study we compared topical metformin with hydroquinone for treating epidermal melasma. Mean age of patients in this study was 41.29±13.01 and 36.16±11.46 respectively. Age of patients ranges between 20-60 years. Mapar MA reported the mean age of patients as 35.52±7.11 years in his study[11] where the mean age was slightly lower when compared with the mean age reported in our study. In an Indian, study age range of melasma patients reported as 23-84 years which was quite higher when compared with the age range of this study.[12] The difference of mean age with other studies may be due to geographical and genetic variations as compared to this region.

Mean duration of melasma for patients in Group-A and B was 20.87±11.64 and 19.23±12.15 respectively. Mean duration of disease reported by Banavase Channakeshavaiah R ranges between 1-108 months.[12] However, duration of disease in our study was quite shorter in comparison to the above study. Mean duration of disease reported by Doaa Abd

Elhameed Atta Shokier was 5 years on average which was quite higher when compared with the results of this study regarding duration of disease.[21]

In Group-A 7 (22.58%) patients and in Group-B 9 (29.03%) patients had family history of melasma. Doaa Abd Elhameed Atta Shokier from Egypt[21] reported family history of melasma among 53.3% patients which was quite higher when compared with this study.

This study results showed that mean percentage reduction in MASI score in Group-A (metformin group) and B (hydroquinone group) was 60.28±14.04 and 55.02±13.35. As per efficacy criteria patients treated with metformin had higher efficacy as compared to patients treated with hydroquinone respectively. i.e. Group-A: 80.6% vs. Group-B: 58.1%, which is significant statistically p-value=0.054. Regarding safety no significant difference was seen for side effects like hypopigmentation and swelling between groups from 1st month till 4th month follow up post treatment.

A clinical study from India compared triple combination cream (HQ 2%, tretinoin 0.025%, and fluocinolone acetonide 0.01%) cream with 30% metformin lotion and showed comparable results in patients in terms of MASI score at 8th week post treatment respectively.[16] In the metformin group no significant side effects were seen in patients while patients treated with triple combination cram cream showed many significant side effects. The difference of side effects between treatment groups was statistically significant (p-value <0 .001).

An Egyptian research evaluated the effectiveness and safety of using silymarin at various concentrations (0.7% and 1.4%) compared to hydroquinone 4% for treating melasma. The findings of this research demonstrated a substantial decrease in the MASI score across all groups after three months. However, there were no notable variations in the treatment response among the three groups under investigation. Silymarin did not exhibit any known side effects, however hydroquinone was shown to be related with notable unfavorable consequences.[17]

In this study mean reduction in MASI score in metformin group was recorded as 60.28±14.04 which is slightly higher as that of reported in above study. Both above mentioned studies reported similar results as that of this study, showing the efficacy of topical metformin for treating melasma patients without any significant side effects.

Lehraiki and colleagues previously observed that metformin, a medication used to treat diabetes, effectively suppressed melanogenesis, both in laboratory settings and in living organisms. They proposed that metformin may be a valuable treatment option for hyperpigmentation. After applying a 30% topical solution of metformin on the tails of mice every day for a period of eight weeks, researchers observed a loss of pigmentation in the tails.[18]

Another quasi experimental study conducted in Egypt showed statistically significant improvement in melasma after treatment with topical metformin at 2nd, 3rd, 4th months of treatment and also one month after treatment. The Melasma Area and Severity Index (MASI) score showed a progressive decline after each session, with mean scores of 13.8, 13.7, 11.5, 11.4, and 11.4, respectively. There was a statistically significant improvement seen after 2, 3, and 1 month(s) after the completion of therapy, with corresponding p-values of 0.002, 0.001, and 0.001, respectively. No side effects were observed however.[21]

Studies have reported no side effects of metformin for treating melasma patients.[16,19,20]

Similar findings were obtained in this study regarding the safety profile of topical metformin.

Recently, it has been indicated that metformin can reduce intracellular cAMP.[21] Metformin seems to decrease melanogenesis via affecting cAMP, which is involved in the process. Metformin causes a significant reduction in the amount of melanin present in the basal layer. Conversely, it contributes to the reduction of tyrosinase enzyme levels, as well as TRP-1 and TRP-2 proteins, which are crucial for melanogenesis. One other explanation for metformin's ability to prevent melanogenesis is its role in reducing expression of microphthalmia-associated transcription factor (MITF) via the cAMP dependent pathway.[22] Systemic use of metformin has not produced these side effects; they have only been noted in topical applications of the medicine. Only in animal models has metformin's efficacy been investigated in the treatment of skin hyperpigmentation.[23]

Conclusion

The present study concluded that efficacy of the topical metformin is better for the treatment of epidermal melasma as compared to 4% hydroquinone. This new modality in the treatment of melasma can improve the quality of life of these patients.

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