Original Article

Study to compare the therapeutic effects and safety of topical 4% hydroquinone and 2% kojic acid cream in the management of moderate-to-severe melasma

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Introduction: Melasma is a common, acquired, and mostly symmetric hyperpigmentation characterized by irregular and light-to-grey to dark-brown macules and patches with well-defined margins. **Objective:** The study aimed to compare the therapeutic effects and safety of topical 4% hydroquinone and 2% kojic acid cream in the management of moderate-to-severe facial melasma. **Methods:** A total 90 patients of facial melasma were selected randomly. Forty-five patients were treated with topical 4% hydroquinone cream and 45 patients were treated with topical 2% kojic acid cream given for bed time application for 4 months and was followed up further 2 months at monthly intervals. Patients were instructed for strict photo-protective measures by applying sunscreen daily. Clinical photographs taken and melasma area and severity index (MASI) scoring was performed at monthly intervals and any adverse effects and complications were recorded at each follow-up. **Results:** In Group A, patients treated with topical 4% hydroquinone cream the mean improvement in MASI score increased from 6.29 at 4th week to 14.94 at 12th week. Furthermore, the percentage improvement increased at each visit from 30.18% at 4th week to 71.68% at 12th week. In Group B, patients treated with topical 2% kojic acid cream the mean improvement in MASI score increased from 6.32 at 4 week to 14.69 at 12th week. Furthermore, the percentage improvement increased at each visit from 27.57% at 4th week to 64.09% at 12th week. **Conclusion:** This study suggests that topical 4% hydroquinone cream may be more effective than topical 2% kojic acid cream in the treatment of moderate to severe facial melasma.

KEY WORDS: Melasma, hydroquinone, kojic acid

INTRODUCTION

Melasma is an acquired disorder of melanogenesis leading to hyperpigmentation and manifests as almost always symmetrical brown to grey-black macules and patches with serrated irregular edges.[1] Melasma affect patients because of the fact that it mainly presents with symptoms on the face also being easily visible and constantly visible in everyday life leads to further discomfort to the patient. To this context, the quality of life of the patients is affected negatively impacting their psychological along with emotional well-being of the patient which often motivate the patients to search for a dermatologist. Patients commonly report feelings of shame, low self-esteem, dissatisfaction, and the lack of motivation to go out.[2]

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The reported prevalence of melasma ranges from 9% in Hispanics in the southern parts of the USA to 40% in South-east Asian groups. Melasma is cited as the most commonly found pigment disorder among Indians and the third most common pigmentary disorder in those with black skin. While the exact

causes remain unknown, it is hypothesized that the condition may be causes by the biologically active melanocytes. A genetic predisposition has been noted in several studies.[3]

Etiologic factors affecting the pathogenesis of the disorder are genetic influences, pregnancy, exposure to UV radiation, hormonal therapies (example oral contraceptives and thyroid hormones), phototoxic drugs, cosmetics, and anti-seizure medications.[4]

For the diagnosis and evaluation of treatment of melasma clinical examination, photography, woods lamp examination, dermoscopy, and confocal microscopy can be done. The severity of melasma could be evaluated using colorimetry, mexametry, and calculation of melasma area severity index (MASI).[5]

On histologic finding of melasma is increase melanin content in the dermis and epidermis but the amount differs with the severity of hyperpigmentation. Majority of the studies manifested no quantifiable rise in melanocytes cell though the melanosomes are more copious and cells are distended with distinguished and broaden dendrites.[6]

On the bases of dispersal of the facial lesions seen in the melasma disorder was originate to be classified into three category malar, centrofacial, and mandibular patterns. Melasma can be classified as epidermal, dermal, mixed, and indeterminate variants on the basis of involvement skin layers by pigmentation.[7]

Treatment of melasma is tough because of its dermal constituent and propensity to recurrence. The most usual therapy in treating melasma is to use broad-spectrum (UVA and UVB) and physical sunscreen.[8] Different techniques such as depigmenting agent hydroquinone, kojic and azelaic acids, tretinoin, glycolic, and trichloroacetic acids are being used but chemical peeling have found to provide extra quick retort related to topical therapy. Chemical peels act by creating injury to the skin at a specific depth and causes exfoliation of skin which in turn stimulates new epidermal growth of skin and collagen for more even distribution of melaninp.[9]

Topical treatments are typically the first-line therapies for melasma, among which hydroquinone is the most widely used depigmenting product and is also considered as gold standard for the management of melasma. However, there are several studies which have pointed out to the long-term side effect to the skin associated with the hydroquinone thus compromising and affecting its use in the skin depigmentation products. Hydroquinone is mostly accompanying with irritant contact dermatitis and exogenous ochronosis.[10]

Kojic acid is a fungal metabolic agent which does not get oxidized in skin lotions. It is a chelation product that is synthesized by some fungi example Aspergillus oryzae. Kojic acid mainly hinders and averts the production of tyrosine and it also has some antimicrobial properties in case of some usual bacterial strains also in small dilutions.[11] Kojic acid is linked with sensitization, irritant contact dermatitis, and erythema.

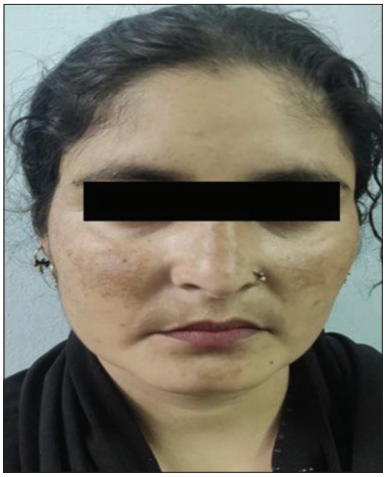

Figure 1: Pre-treatment photograph in Group A

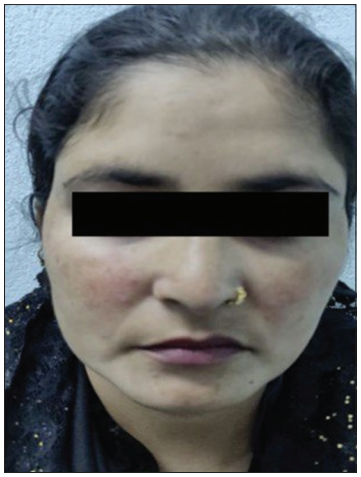

Figure 2: Post-treatment photograph in Group A

The aim of this study was to evaluate the therapeutic effect of topical 4% hydroquinone cream versus topical 2% kojic acid cream in the management of patients with moderate-to-severe facial melasma.

MATERIALS AND METHODS

Our study was carried out in the outpatient department of dermatology, venereology, and leprosy, Rohilkhand Medical College and Hospital, Bareilly, U.P from November 1, 2020, to October 31, 2021. This was a randomized and clinical trial type of study. Inclusion criteria included those who are willing for study, moderate-to-severe melasma, age (19–60) years, mentally stable, oriented, and coherent patients with realistic expectation. Exclusion criteria included pregnancy and lactation, melasma inducing drugs, patients on photosensitizing drugs or thyroid hormones, and patients on hormone replacement therapy. All the eligible patients who had attended outpatient department (OPD) during the study period were enrolled for the study. Sample size of 90 (45 in Group A – On topical hydroquinone 4% cream and 45 in Group B – On topical Kojic acid 2% cream) was taken.

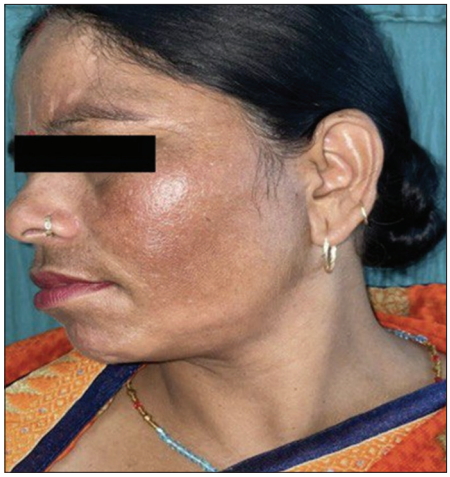

Figure 3: Pre-treatment photograph in Group B

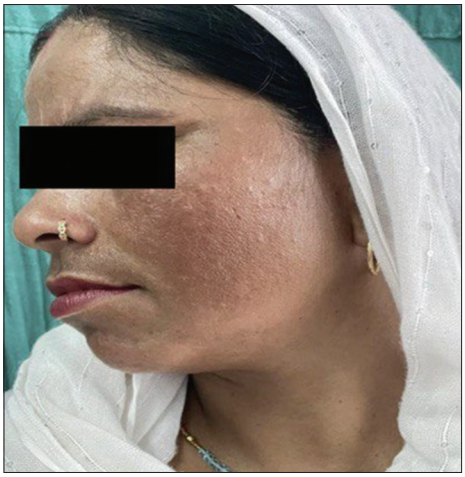

Figure 4: Post-treatment photograph in Group B

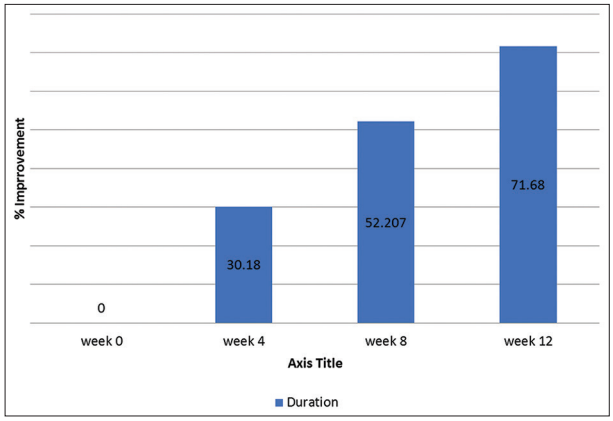

Figure 5: Percentage improvement in melasma area severity index score in Group A (4% hydroquinone cream)

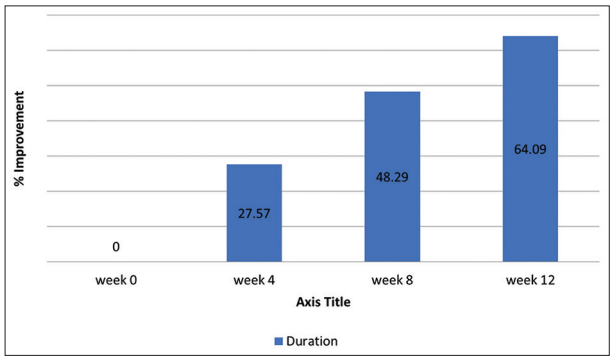

Figure 6: Percentage improvement in melasma area severity index score in Group B (2% kojic acid cream)

Intervention Procedure

IEC approval was taken before start of the study. A written consent was taken from the patient selected for the study according to inclusion and exclusion criteria. A detailed clinical history and examination with respect to melasma was done and noted in the case recording form.

In Group A, before application of 4% hydroquinone cream, a patch test was performed on patients and after getting negative patch test a topical cream of 4% hydroquinone was given for bed time application for 4 months and was followed up further 2 months at monthly intervals. Patients were instructed for strict photoprotective measures by applying sunscreen daily (Figures 1 and 2). In Group B, before application of 2% kojic acid cream a patch test was performed on patients and after getting negative patch test a topical cream of 2% kojic was given once daily preferably at night for 4 months and was followed up further 2 months at monthly intervals. Patients were instructed for strict photo-protective measures by applying sunscreen daily (Figures 3 and 4).

To assess the clinical response in both groups, clinical photographs were taken at the beginning of the therapy and then serially every month. Melasma Area and Severity Index (MASI) scoring was performed at monthly intervals and any adverse effects and complications were recorded. The MASI scoring assesses the severity of melasma in four regions (forehead, right malar region, left malar region, and chin) based on three variables: Percentage of total area involved (A), darkness (D), and homogeneity (H). Numerical value assigned for the corresponding percentage area involved is as follows. The area (A) of melasma involvement is graded from 0 to 6, 0 = No involvement, 1 ≤ 10% involvement, 2 = 10–29% involvement, 3 = 30–49% involvement, 4 = 50–69% involvement, 5 = 70–89% involvement, and 6 = 90–100% involvement. The darkness of pigmentation (D) and homogeneity (H) graded from 0 to 4. 0 = Absent 1 = Slight, 2 = Mild, 3 = Marked, and 4 = Maximum. MASI score was calculated by taking the sum of the severity grade for darkness (D) and homogeneity (H), multiplied by the total areas of the region (A) involved and the percentages of the four facial regions (10-30%). Total MASI = Forehead 0.3 (D + H) A + Right malar 0.3 (D + H) A + Left malar 0.3 (D + H) A + Chin 0.1 (D + H) A.

Statistical analysis done by coding, entry of the data, its clearing, and compiling will be done in Excel sheets. Appropriate statistical software, including SSPS (Statistical Package for the Social Sciences) version 23 was used for statistical analysis.

Table 1: Effectiveness within the group

Group	MASI score	N	Minimum	Maximum	Mean	Standard deviation	Median	Anova F	*P* value
Group- A (4% hydroquinone cream)	Week 0	45	8.6	43	20.84	8.98	18	37.207	<0.001*
	Week 4	45	6	36.5	14.55	7.46	11		
	Week 8	44	3	31	9.95	6.42	7.5		
	Week 12	44	1.2	28	5.84	4.80	4		
Group- B (2% kojic acid cream)	Week 0	45	8.4	42	22.92	7.23	22.2	31.681	<0.001*
	Week 4	45	5	38.4	16.60	7.21	16.2		
	Week 8	44	4	35.4	11.76	7.48	9.25		
	Week 12	43	1	28	8.78	7.52	4.4		

RESULTS

In our study, out of 90 patients, 71 patients (78.9%) were female, while 19 patients (21.1%) were male. An overall female preponderance was noticed with the female to male ratio being 3.73:1. In each group, 12 male patients (26.66%) and 33 female patients (73.33%) received 4% hydroquinone cream (Group A) and 7 male (15.55%) and 38 female (84.44%) patients received 2% kojic acid cream (Group B). Maximum patients in our study were of age group 19–29 years (38.88%), and minimum were those of age group 50–60 years (4.44%). The majority of patients in our study were of epidermal melasma constituting 50% of total cases, while dermal type and mixed type of melasma constituted only 5.55% and 44.44%, respectively. On asking the duration of disease, most patients (55.57%) were found to be dealing with it for <2 years, followed by patients with disease duration of more than 5 years (26.65%), and only 15 patients (17.78%) had it for 2–5 years.

The mean improvement in MASI score increased from 6.29 at 4 weeks to 14.94 at 12 weeks. Furthermore, the percentage improvement increased at each visit from 30.18% at 4 weeks to 71.68% at 12 weeks. The mean improvement in MASI score increased from 6.32 at 4 weeks to 14.69 at 12 weeks (Table 1). Furthermore, the percentage improvement increased at each visit from 27.57% at 4 weeks to 64.09% at 12 weeks. The change in MASI score was statistically significant ($P < 0.001$*) at every week. Hence, on collating the results of group A and B, improvement was from 30.18% at 4 weeks to 71.68% at 12 weeks in Group A while 27.57% at 4 weeks to 64.09% at 12 weeks in Group B (Figures 5 and 6) . Overall improvement was more in Group A compared to Group B. In Group A (4% Hydroquinone cream), three patients complained of erythema, two patients had burning sensation, one patient developed itching, and one patient experienced skin dryness. In Group B (2% kojic acid cream), one patient had erythema, one patient presented with skin dryness, and one patient complained of itching.

DISCUSSION

Melasma occurs in the middle age adults and is more commonly seen in females. Majority of the patients with melasma were found to be in the age group 19–29 years, total contributing 38.8% of total patients. This was similar to the finding in the study by Griffiths *et al.* in which the mean age of onset was 30 years.[12]

A study by Vazquez *et al*. showed 60 years, contributing only (4.4%) of total patients presenting in OPD for melasma treatment. The reason for the older age group presenting less in OPD could be that they are no more cosmetically concerned about the disease or they are tired of undergoing treatment repeatedly because of its recurrence nature.[13]

The female preponderance is attributed mainly due to hormones factors. Our study showed a higher number of female cases, female to male ratio was observed to be 3:1. This observation is unlike as shown in a study by Achar and Rathi where the ratio was around 4:1.[2]

Centrofacial pattern was the most common type in our study present in 43.3% of the patients followed by malar in 40% and least was the mandibular type with 16.6% of the cases. This result was similar to study by Shankar *et al.* where 42% of patients had centrofacial type, followed by 42% of malar and least cases belong to mandibular type of melisma. A similar finding by Vazquez *et al*. showed equal occurrence of centrofacial and malar pattern (41.1%) and mandibular pattern was the least common (11.1%). A similar result was exhibited in a study by Sarkar *et al.* with maximum centrofacial type (48.39%). Similarly, Griffiths *et al*. showed that centrofacial was the predominant pattern of involvement.[12]

With the help of wood's lamp examination, the epidermal type was the most common with 50%, which was followed by dermal melasma in 5.5% of patients and 44.4% of cases of mixed type. This collated with observations made by Kavya M, with the epidermal type being the most common with 55.5% of incidence.[14] Similar were the findings in a study by Yalda *et al*. in which 40% of patients of melasma were of epidermal type, 34% dermal type, while 26% of mixed type.[15] However, a study by Achar and Rathi showed dermal more with 54.48% followed by 21.67% of epidermal type.[2]

All the patients are known to have sun exposure. About 42.22% of patients were exposed in between 1 and 2 h of sun exposure, 31.11% of patients had >2 h and 26.66% of patients had <1 h of daily radiation from the sun. Griffith CE in their study showed sun to be exacerbating factor in 98% of cases.[12] The reason for the epidermal type being the most common could be that since most of patients in our study were exposed to UV radiations for 1–2 h, the ultraviolet rays induced damage could not reach dermis and only damage the epidermis.

There have been several studies comparing the efficacy of different hypopigmenting agents. Review of literature shows only few studies were done by Monteiro (2013), Sukumar (2016) and Joshua (2020) comparing HQ and KA as individual drugs else there were no other study conducted for comparing the efficacy of HQ and KA.[16] A study by Garcia and Fulton comparing HQ and KA but both drugs used in combination of glycolic acid.[17]

At 4th, 8th, and 12th week of post-treatment evaluation of MASI, the mean change in MASI following application of 2% KA was less than that of 4% HQ, which was statistically highly significant (16.60, 11.76, 8.78, and 14.55, 9.95, and 5.84, respectively, $P < 0.001$). These results were in contrast to those with Garcia and Fulton[17] where in glycolic acid with 5% KA showed better efficacy (28%) compared to glycolic acid with 5% HQ (21%); however, their results were not statistically unlike ours where there was a statistically highly significant difference between HQ and KA, the former being better. The possible explanation for this could be that the addition of glycolic acid might have potentiated the action of kojic acid. At 4th week in Group A, the mean MASI was 14.55 at 4 weeks, with a change in MASI being 6.29, that is, 30.18% improvement. In Group B, the mean MASI was 16.66 with a change in MASI being 6.3, that is, 27.57% improvement. At 12th week in Group A, the mean MASI was 5.84, with the change in MASI being 14.94, that is, 71.68% improvement. In Group B, the mean MASI was 8.78, with change in MASI being 14, that is, 64.09% improvement in Group B.

Clearly, improvement is more in Group A compared to Group B, indicating that the 4% of hydroquinone is better topical agent in the treatment of melasma when compared to 2% kojic acid. In this study, 4% of hydroquinone was associated with slightly higher side effects compared to 2% kojic acid (15.55% vs. 3.33%). Redness, stinging, and exfoliation were the most common side effects noted by Lim *et al*. in patients receiving hydroquinone and kojic acid. Erythema was seen in three patients with 4% hydroquinone and one patient with 2% kojic acid. Two patients complaining of burning sensations after applying 4% hydroquinone and was not seen in patients with 2% kojic acid. However, the side effects with 2% kojic acid was temporary and resolved with continued treatment, whereas one patient on 4% hydroquinone with erythema discontinued the treatment. Overall, the side effect rate was not statistically significant. Redness, stinging, and exfoliation were the most common side effects noted by Lim *et al*. and Chan *et al*. which were not significant in both sides.[18,19]

CONCLUSION

The results of this study show that both 4% hydroquinone and 2% kojic acid are effective topical hypopigmenting agents in the management of moderate-to-severe facial melasma. About 4% of hydroquinone is a better topical hypopigmenting agent with rapid rate of clinical improvement when compared to 2% kojic acid. The adverse effects of both the hypopigmenting agents were not significant.

REFERENCES

1. Sarkar R, Arora P, Garg VK, Sonthalia S, Gokhale N. Melasma update. Indian Dermatol Online J 2014;5:426-35.
2. Achar A, Rathi SK. Melasma: A clinico-epidemiological study of 312 cases. Indian J Dermatol 2011;56:380-2.
3. Rodrigues M, Pandya AG. Melasma: Clinical diagnosis and management options. Australas J Dermatol 2015;56:151-63.
4. Farshi S. Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma. J Cosmet Dermatol 2011;10:282-7.
5. Arrowitz C, Schoelermann AM, Mann T, Jiang LI, Weber T, Kolbe L. Effective tyrosinase inhibition by thiamidol results in significant improvement of mild to moderate melasma. J Invest Dermatol 2019;139:1691-8.e6.
6. Grimes PE, Ijaz S, Nashawati R, Kwak D. New oral and topical approaches for the treatment of melasma. Int J Womens Dermatol 2019;5:30-6.
7. De Abreu L, Ramos-E-Silva M, Quintella LP, Buçard AM, Bravo BS, De Almeida AM, *et al*. Dermoscopic classification of melasma: Concordance study and correlation with the melanophages count. J Cosmet Dermatol 2022;21:5887-64.
8. Rendon M, Berneburg M, Arellano I, Picardo M. Treatment of melasma. J Am Acad Dermatol 2006;54(5 Suppl 2):S272-81.
9. Dangi S, Kothiwala R, Meherda A. Comparative study of efficacy and safety of lactic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Clin Dermatol 2018;1:83-36.
10. Bronzina E, Clement A, Marie B, Chong KT, Faure P, Passeron T. Efficacy and tolerability on melasma of a topical cosmetic product acting on melanocytes, fibroblasts and endothelial cells: A randomized comparative trial against 4% hydroquinone. J Eur Acad Dermatol Venereol 2020;34:897-903.
11. Owolabi JO, Fabiyi OS, Adelakin LA, Ekwerike MC. Effects of skin lightening cream agents-hydroquinone and kojic acid, on the skin of adult female experimental rats. Clin Cosmet Investiga Dermatol 2020;13:283-9.
12. Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. Br J Dermatol 1993;129:415-21.
13. Vázquez M, Maldonado H, Benmamán C, Sanchez JL. Melasma in men: A clinical and histologic study. Int J Dermatol 1988;27:25-7.
14. Kavya M. Melasma: A clinico-epidemioological study. Int J Basic Appl Med Sci 2014;4:388-91.
15. Nahidi Y, Meibodi NT, Layegh P, Esmaeeli H, Hosseini FS. Evaluation of the relationship between clinic-epidemiological features of melasma and the level of involvement on wood's lamp examination. Iran J Dermatol 2013;16:57-63.
16. Monteiro RC, Kishore BN, Bhat RM, Sukumar D, Martis J, Ganesh HK. A Comparative study of the efficacy of 4% hydroquinone vs 0.75% kojic acid cream in the treatment of facial melasma. Indian J Dermatol 2013;58:157.
17. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. Dermatol Surg 1996;22:443-7.
18. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999;25:282-4.

19. Chan R, Park KC, Lee MH, Lee ES, Chang SE, Leow YH, *et al*. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0·01%, hydroquinone 4%, tretinoin 0·05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Br J Dermatol 2008;159:697-703.