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Original Article

Comparison of the efficacy and safety of topical 4% hydroquinone cream vs topical 10% glutathione plus 5% ascorbic acid cream in patients with epidermal melasma

局部4%對苯二酚乳膏與局部10%穀胱甘肽加5%抗壞血酸乳膏在表皮黃褐斑患者中的療效和安全性比較

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Objectives: This study compared the efficacy and safety of topical 4% hydroquinone cream vs topical 10% glutathione plus 5% Ascorbic acid cream in patients of epidermal melasma. ***Method:*** This was a randomized controlled trial in which seventy patients were enrolled according to inclusion criteria and randomly divided into two groups containing thirty-five patients in each group. The patients in Group A were given topical 4% hydroquinone cream daily at night while those in Group B were given combination of topical 10% glutathione plus 5% ascorbic acid cream daily at same time. Treatment was continued for sixteen weeks and follow up done for eight weeks after last treatment. Efficacy was assessed at the end after twenty-four weeks. Side effects were observed on every visit. ***Results:*** The mean reduction in Melasma Area Severity Index (MASI) score in Group-A was 53.88±18.36% and in Group-B 39.66±14.53%. The mean reduction in MASI score was significantly higher in Group-A when compared to Group-B. ***Conclusion:*** Topical 4% hydroquinone cream is more effective but had more side effects as compared to combination of 10% glutathione plus 5% ascorbic acid cream for epidermal melasma in Asian skin types.

目的：本研究旨在比較局部 4 %對苯二酚乳膏與局部 10 %穀胱甘肽加 5 %抗壞血酸乳膏對表皮黃褐斑患者的療效和安全性。**方法**：這是一項隨機對照試驗，其中根據納入標準招募了 70 名患者，並將其隨機分為兩組，每組各 35 名患者。 A 組患者每天晚上局部給予 4 %對苯二酚乳膏， B 組患者每天同樣時間局部給予 10 %穀胱甘肽加 5 %抗壞血酸乳膏聯合用藥。連續治療十六週，並在最後一次治療的八週後覆診，合計二十四周後評估療效。每次訪問均有監測副作用。**結果**：A 組的黃褐斑面積和嚴重程度指數得分平均降低了 53.88±18.36 %， B 組該指數則平均降低了 39.66±14.53 %。 A 組的黃褐斑面積和嚴重程度指數得分平均降低幅度明顯較 B 組為高。**結論**：與 10 %穀胱甘肽加 5 %抗壞血酸乳膏聯合治療相比，局部 4 %對苯二酚乳膏對亞洲皮膚人士的表皮黃褐斑相更為有效，但副作用亦更多。

Keywords: Epidermal Melasma, Glutathione, Hydroquinone

關鍵詞：表皮黃褐斑、穀胱甘肽、對苯二酚

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Introduction

Melasma presents as an acquired irregular light to dark brown usually symmetrical facial hyperpigmentation, that commonly affects females particularly who have frequent exposure to ultraviolet (UV) rays.[1] The incidence of melasma is reported as high as 4-10% of new case referrals and mostly affects Hispanic and Asian populations.[2]

The exact aetiology of melasma is still unknown, although it is influenced by genetic and hormonal factors as well UV-rays. Oestrogen replacement therapy, contraceptive pills, ovarian tumours or dysfunction, thyroid disorders, make-up products, food, photo-allergic and phototoxic medicines are some of the contributing factors of melasma.[3] It most frequently affects darker skin people (Fitzpatrick skin types IV-VI). There are three major patterns of distribution: centro-facial (forehead, nose, cheeks, upper area of lip), mandibular and malar (nose and cheeks). Melasma is categorised into three types: epidermal, dermal and mixed according to its clinical appearance under Wood's lamp.[3,4]

The major causative agent is sun exposure, hence the use of broad-spectrum sunscreens is the first-line management along with depigmenting agents for sun protection.[3] The most commonly used topical therapy for melasma is hydroquinone which is considered to be the gold standard. Other options include tretinoin, corticosteroids, ascorbic acid, azelaic acid and arbutin. Triple combination of hydroquinone, tretinoin and steroids is also used. Different types of peels like salicylic acid, glycolic acid, retinoic acid and kojic acid have also been tried. However, more research is needed for several other topical agents such as niacinamide, flavonoids, liquorice derivatives and N-acetyl glucosamine as data for their roles as depigmenting agent is limited.[5]

These treatment options have their side effects, especially after prolonged use, as well as being of limited efficacy with frequent relapse on discontinuation of therapy. As there is no permanent cure for melasma, research is ongoing for a newer effective and safer agents for treating this pigmentary disorder.[6,7]

Hydroquinone (HQ) is a commonly used depigmenting agent in epidermal type of melasma. It is hydroxyphenolic compound which acts on enzyme tyrosinase which inhibits the process of dihydroxyphenylalanine (DOPA) conversion into melanin. It causes necrosis of melanocytes by affecting their membrane structure. Commonly seen side effects are irritation, post-inflammatory hyperpigmentation, erythema, stinging, and allergic contact dermatitis.[8]

The production of melanin (melanogenesis) is inhibited by ascorbic acid, also recognised as vitamin C. It interacts with copper at the tyrosinase active site and blocks dihydrochinindol-2-carboxyl acid oxidation that decreases dopaquinone.[9]

Glutathione is a protein constituted by three amino acids; glycine, cysteine and glutamic acid. It is an antioxidant and reduces skin hyperpigmentation. The production and agglutination of melanin is inhibited by glutathione through disturbing the physiological function of L-DOPA.[10] Vitamin C when combined with glutathione augments the effect of glutathione.[11]

There has been much research on these drugs as treatments for melasma. Hydroquinone is effective but with side effects in almost 68.7% of patients.[12] Similarly glutathione has been tried and effective results seen in different studies.[13-15] As these agents have not been compared in our part of the world, this study was performed to consider effective and safe alternatives to hydroquinone in the treatment of melasma.

Materials and methods

Seventy patients were recruited according to the following inclusion criteria: patients with epidermal melasma diagnosed on Wood's lamp examination, patients over 15 years of age, area of distribution: centro-facial, malar, mandibular, involving face with MASI score ranging 6-35, Fitzpatrick skin type III, IV and V as determined by two qualified dermatologists from the dermatology department of Mayo Hospital, Lahore. After taking written and informed consent and recording demographic data, complete history was taken and examination performed. Baseline investigations (haemoglobin, serum creatinine, SGPT level), TSH level and urine for pregnancy test in married females were performed to rule out any underlying systemic disease or pregnancy. The information was collected through specially designed proforma. The type of melasma was identified using Wood's lamp. Only patients with epidermal type were selected for treatment. MASI score was calculated before starting of treatment and each visit. All the subjects were instructed to use sunscreen with SPF 30 for photo-protection throughout the day for the period of treatment and follow-up.

The patients were divided into two groups, A and B (thirty-five patients in each group) randomly by using computer generated random number table. Group A was advised to apply 4% hydroquinone and Group B to apply combination of 10% glutathione plus 5% ascorbic acid daily at night onto the affected area. Treatment was continued for 16 weeks and patients were followed up for eight weeks after the last treatment. Female, married patients included in study were counselled on proper contraception and they were advised against pregnant throughout this period. Final evaluation was done at the end of 24 weeks.

Results were evaluated clinically by single blinded two qualified dermatologists and calculated by percentage reduction in MASI score. Patients were examined for any side effects during the duration of treatment. Digital photographs taken before and at the end of treatment were compared. Only patients who completed the treatment till last follow-up were included in the evaluation data.

Data analysis

SPSS version 20 was used to enter and analyse the collected data. Quantitative variables like age and MASI score were presented by using mean±SD. The frequency tables, percentages and appropriate graphs were used to illustrate the qualitative variables like gender. Efficacy and side effects in both treatment groups were evaluated by using Chi-square test. A p-value of ≤ 0.05 was considered significant.

Results

Seventy patients were enrolled (35 in each group). In Group A there were 3 (8.57%) male and 32 (91.43%) female cases while in Group B there were 2 (5.71%) male and 33 (94.29%) female cases. The difference in gender distribution in both groups was not significant. The mean age of patients was 29.09±5.33 years in Group A and 27.69± 4.28 years in Group B.

At baseline the mean MASI scores in Group A and Group B were 11.96±6.81 respectively. At 4th week mean MASI score in Group A and Group B were 10.25±5.96 and 11.29±6.45 respectively. At 8th week mean MASI score in Group A and Group B were 8.68±5.56 and 9.89±5.74 respectively. The mean MASI at each visit was statistically same in both study groups, $p<0.05$ (Table 1). At 12th week mean MASI score in Group A was 7.32±5.03 and Group B was 8.53±4.96 respectively, mean MASI score at 16th week in Group A was 6.27±4.87 and Group B, 7.74±4.61, at 20th week mean MASI score in Group A and Group B was 6.49±4.81 and 7.93±4.62 respectively and mean MASI score

24th week at Group A and Group B was 6.64± 4.81 and 8.23±4.68 respectively. The mean MASI score at each follow up was same, $p<0.05$.

The mean reduction in MASI score in Group A was 53.88±18.36% and in Group B 39.66±14.53% (Table 2). The mean reduction in MASI score was significantly higher in Group A when compared to Group B, $p<0.05$ (Figure 1).

The efficacy in both the group was also compared as poor (0-25%), fair (26-50%), good (51-75%) and excellent (more than 75%). The results are shown in Table 3.

While comparing the safety profile, only four patients observed side effects among Group B as compared to Group A, where 21 patients had observed side effects. Comparison of safety profile is plotted in Table 4.

Table 1. Comparison of MASI score at different follow ups in both study groups

			95% CI for mean		
	Mean	**SD**	**Lower bound**	**Upper bound**	**p-value**
MASI (baseline)					0.586
Group A	11.96	6.81	9.62	14.30	
Group B	12.88	7.29	10.38	15.38	
Total	12.42	7.02	10.75	14.09	
MASI (4th week)					0.482
Group A	10.25	5.96	8.20	12.29	
Group B	11.29	6.45	9.08	13.51	
Total	10.77	6.19	9.30	12.24	
MASI (8th week)					0.374
Group A	8.68	5.56	6.77	10.59	
Group B	9.89	5.74	7.92	11.86	
Total	9.28	5.64	7.94	10.63	
MASI (12th week)					0.316
Group A	7.32	5.03	5.59	9.05	
Group B	8.53	4.96	6.82	10.23	
Total	7.92	4.99	6.73	9.11	
MASI (16th week)					0.197
Group A	6.27	4.87	4.59	7.94	
Group B	7.74	4.61	6.16	9.32	
Total	7.00	4.77	5.87	8.14	
MASI (20th week)					0.206
Group A	6.49	4.81	4.84	8.14	
Group B	7.93	4.62	6.34	9.51	
Total	7.21	4.73	6.08	8.34	
MASI (24th week)					0.167
Group A	6.64	4.81	4.99	8.29	
Group B	8.23	4.68	6.62	9.83	
Total	7.43	4.78	6.29	8.57	

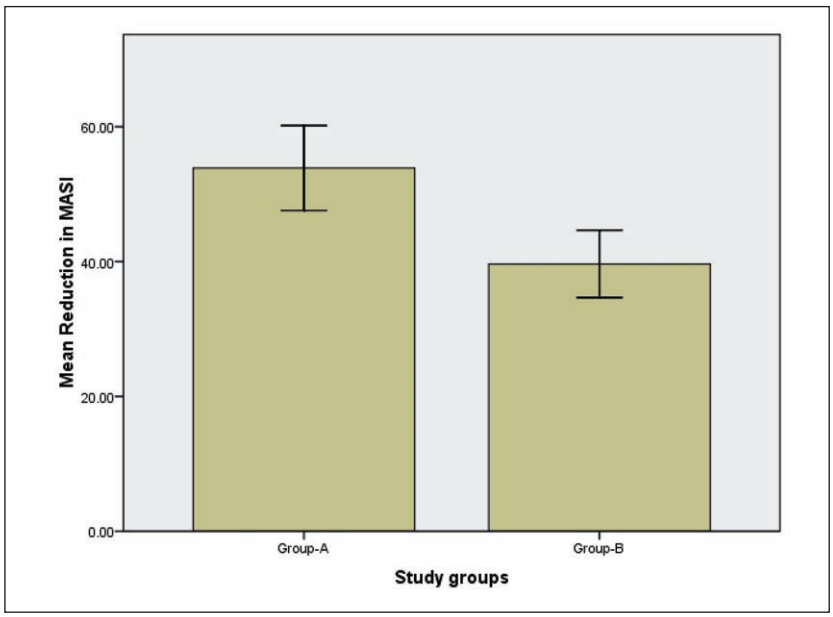

Figure 1. Comparison of mean reduction (%) in both study groups

Table 2. Comparison of reduction in MASI in both study groups

			95% CI for mean		
	Mean	**SD**	**Lower bound**	**Upper bound**	**p-value**
Reduction in MASI (%)					0.001
Group A	53.88	18.36	47.57	60.19	
Group B	39.66	14.53	34.67	44.65	
Total	46.77	17.93	42.49	51.04	

Table 3. Comparison of efficacy in both study groups

	Study groups		
	Group-A	**Group-B**	**Total**
Efficacy			
Poor (up to 25%)	1 2.9%	5 14.3%	6 8.6%
Fair (26-50%)	14 40.0%	21 60.0%	35 50.0%
Good (51-75%)	11 31.4%	8 22.9%	19 27.1%
Excellent (76-100%)	9 25.7%	1 2.9%	10 14.3%
Total	35 100.0%	35 100.0%	70 100.0%

Chi-square = 10.94
p-value = 0.012

Table 4. Comparison of side effects in both study groups

	Study groups		
	Group-A	**Group-B**	**p-value**
Side effects			
Burning	2 9.52%	0 0%	0.151
Stinging	0 0%	1 33.3%	0.314
Irritation	1 4.76%	0 0%	0.314
Itching	4 19.04%	0 0%	0.039
Redness	10 47.61%	2 66.7%	0.011
Dryness	4 19.04%	1 33.3%	0.164
Total	21 (100%)	4 (100%)	

Discussion

Melasma is a common acquired pigmentary condition in Asians and is exceptionally difficult to treat. The pathogenesis involves hyperplasia of melanocytes and increased activity of melanogenic enzymes. Kang et al[16] have reported that melanocyte hyperfunction is induced by specific melanocytes clones which are triggered by UV rays under the hormonal influence of female and hereditary factors.[16] Thus, newer drugs are required that inhibit production of melanin.

Hydroquinone is a topical depigmenting agent used in the treatment of melasma. It is tyrosinase inhibitor and is believed to have additional actions such as melanosomes disintegration, melanocytes degradation and prevention of the production of DNA and RNA.[17,18] These additional actions probably enhance its action as a skin lightening agent compared to previously used agents. Hydroquinone when used as a sole agent has been found to be efficacious with total improvement rates of melasma in "38%", "77%" and "75%" of patients in different studies.[19-21] Previous studies have reported adverse effects such as pruritus, irritation and contact allergies. Exogenous ochronosis is a sporadic side effect. Therefore, to find similar efficacy and prevent significant side effects, many drugs have been studied for treatment of melasma.

Glutathione has recently been used as skin whitening agent. It also acts as depigmenting agent and reduces melanogenesis by directly inhibiting tyrosinase activity by attaching to the copper-containing active site of the enzyme, facilitating the alteration procedure from eumelanin to phaeomelanin synthesis, removing the free radicals and peroxides that play role in the activation of tyrosinase and melanin production as well as modification of depigmenting properties of melanocytotoxic agents. However, clinical trials on the topical use of glutathione in melasma treatment and its efficacy are lacking. There are no reported studies so far which compare the efficacy of hydroquinone and glutathione with vitamin C and our study is the first in this context.

In our study, glutathione compound was combined with 5% vitamin C. Ascorbic acid inhibits the synthesis of melanin with a decline in melanin oxidisation. On the other hand, it is unable to penetrate into the deeper parts of the skin when used alone. Thus, to address this issue iontophoresis is most frequently used.[21] Vitamin-C is also combined with different skin lightening products. Hence, the glutathione efficacy in our study may have been accelerated by vitamin-C.

In our study the mean age of patients was 29.09±5.33 years in Group A and 27.69±4.28 years in Group B, the age distribution in both groups was statistically same which is comparable with the study performed by Perez-Bernal et al,[12] in which comparison of topical hydroquinone was done with only ascorbic acid, the mean age of patients was 36±8 years. This is because many young individuals consulting for treatment of melasma have more sun exposure and are more beauty conscious.

In our study, we enrolled epidermal melasma patients after Wood's lamp examination as this type of melasma was most responsive to topical treatment. Glutathione was previously considered a skin-whitening agent and its role in melasma has not been extensively studied. We used the epidermal type to evaluate its effect.

In our study, there were total five males and 65 female cases in our study i.e; 7.14% of total number of patients and 92.86% respectively. Out of these, there were three males (8.57% cases) and 32 females (91.43% cases) in Group A and 2 males (5.71% cases) and 33 females (94.29% cases) in Group B. An overall female preponderance was noticed, male to female ratio being 1:13 which is much more compared to other international studies.[21] It shows that females are more concerned about their appearance. It may be that male patients presenting in our outpatient

department had poor follow up or poor referral system.

In our study, mean reduction in MASI score in Group-A was 53.88±18.36% and in Group-B 39.66±14.53%, the mean reduction in MASI score was considerably increased in Group-A when compared to Group-B but mean MASI score at each follow up was statistically same in both study groups.

In Group A, 57.1% had good to excellent efficacy while Group B had 25.8% efficacy. Group A had significantly higher efficacy when compared to Group B which is much less than that of the study conducted by Perez-Bernal et al[12] in which Group A had showed up to 93% efficacy and Group B up to 62.5% efficacy with the use of ascorbic acid only.

In our study, in Group A 65% patients experienced various side effects while in Group B only 11.4% patients had side effects. This is comparable to the findings of Perez-Bernal et al which showed 68% side effects with hydroquinone use and only 6% side effects with use of topical ascorbic acid only.[12] So it showed that hydroquinone had more side effects as compared to glutathione which had less side effects when used as a depigmenting agent.[22]

Other factors likely to contribute to the difference in clinical outcome include the geographical conditions of Pakistan i.e. long duration of summer season and excessive UV light exposure. Use of substandard cosmetics, poverty, poor nutritional status of patients, illiteracy and non-adherence to the regular use of sunscreen could be important contributory factors.

From the above discussion, it is concluded that topical 4% hydroquinone is a better depigmenting agent in epidermal melasma when compared to 10% glutathione plus 5% ascorbic acid but have a higher incidence of side effects than 10% glutathione combined with ascorbic acid.

In addition to topical and physical therapies for melasma, sun protection, patient education and daily use of sunblock should form the basis of treatment in this problematic condition. More studies are required to establish the optimal treatment parameters and to determine the biological mechanisms of the treatments.

Conclusion

Our study has shown that topical 4% hydroquinone cream is more efficacious in the treatment of epidermal melasma in our patient population when compared to a combination of topical 10% glutathione plus 5% ascorbic acid cream but has a higher frequency of side effects.

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