Original Article

Comparison of Topical Silymarin with Hydroquinone in the Treatment of Melasma

Sumaira Abdullah[1], Mahwish Ahmed[2], Mahvish Aftab Khan[3], Tayaba Iqbal[4], Shawana Sharif[5], Farhat Rehman[6]

[1] Assistant Professor, Department of Dermatology, Islamabad Medical and Dental College, Islamabad.
[2] Assistant Professor, Department of Dermatology, HBS Medical and Dental College, Islamabad.
[3] Assistant Professor, Department of Dermatology, Rawal General and Dental Hospital, Islamabad.
[4] Consultant Dermatologist, Leighton Hospital, Crewe, England.
[5] Assistant Professor, Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi.
[6] Postgraduate Trainee, Department of Dermatology, Islamabad Medical and Dental College, Islamabad.

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[2,3,6] Facilitation and Material analysis

Corresponding Author
Dr. Mahvish Aftab Khan,
Assistant Professor,
Department of Dermatology,
Rawal General and Dental Hospital,
Islamabad
Email: mahvishaftabkhan@gmail.com

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Abstract

Objective: To compare the efficacy and safety of topical silymarin 0.7% with topical hydroquinone 4% in the treatment of melasma.

Place and Duration: This Randomized Controlled Trial was conducted at the dermatology OPD of Akbar Niazi Teaching Hospital, Bara Kahu, Islamabad, for a period of one year from April 2020 to April 2021.

Materials and Methods: Female patients having melasma were included in the study. The severity of melasma was assessed using the MASI score. Group A was treated with silymarin 0.7% cream and group B was treated with topical hydroquinone 4% cream. Treatment was given for 3 months and was followed up for the next 3 months to observe relapse. Clinical efficacy was assessed in terms of the percent reduction in MASI score from baseline.

Results: The mean age in group A (Silymarin 0.7%) was 35.13 ± 3.87 and in group B (Hydroquinone 4%) was 34.16 ± 3.90. Epidermal type of melasma was most common (76.8% vs 62.5%) in both groups. There was no significant (p-value > 0.05) difference between both groups after one and two months of treatment but the mean MASI score of the Hydroquinone 4% group (10.59 ± 5.74) became significantly (p-value < 0.05) less than Silymarin 0.7% group (8.20 ± 4.41) after 3 months. Similar (p-value > 0.05) therapeutic response was observed after one and two months of treatment but it became significantly better in Hydroquinone 4% group after three months of treatment. Significantly (P-value < 0.05) higher adverse effects were detected in patients treated with hydroquinone. There was no significant difference (P-value > 0.05) in recurrence rate and patients satisfaction between both groups.

Conclusion: Topical silymarin has comparable efficacy for the treatment of melasma with comparatively very less adverse effects as compared to hydroquinone.

Keywords: Melasma, Silymarin, Hydroquinone, MASI score.

Introduction

Melasma, a notoriously difficult to treat the condition, is a very common cause of facial hyperpigmentation, the incidence, and prevalence of which vary according to different geographical areas, age groups, and skin types.[1]

Melasma has a multifactorial origin with both genetic and environmental factors playing an important role. The exact etiopathogenesis of melasma remains difficult to find, but new techniques like dermoscopy, immunohistochemistry, and in vivo reflectance confocal microscopy have provided sufficient insight into its pathogenesis. The important attributing factors include female sex, pregnancy, contraceptive pills, darker skin types, exposure to ultraviolet light, and positive family history.[1,2]

Melasma presents as light brown to muddy brown facial patches, affecting millions of people across the globe. The three most important facial patterns are centrofacial, malar, and mandibular.[3] It is a therapeutically challenging condition with significant psychological implications. Reduction in pigmentation is obtained by using chemicals that interfere with various steps in melanogenesis. Commonly used topical agents include hydroquinone, kojic acid, azelaic acid, and tretinoin.[4] Tranexamic acid, vitamin C, vitamin E, and certain natural extracts are used as adjunctive therapies. Certain interventional techniques like chemical peels, lasers, intense pulsed light, and microdermabrasion are also used to treat melisma.[4,5]

Hydroquinone is the preliminary depigmenting agent used to treat melasma. It inhibits tyrosinase, the rate-limiting enzyme in melanogenesis. It also causes apoptosis of melanocytes. It is used as an effective monotherapy in the concentration of 2% to 4% but with high concentrations, there is an increased risk of erythema and long-term use (6 months or more than 6 months) of hydroquinone may lead to exogenous ochronosis.[6]

Silymarin is a flavonoid and is obtained from seeds and fruits of milk thistle (Silburn marianum L.Gaerth). It inhibits L-dihydroxyphenylalanine (L-DOPA) oxidation activity of tyrosinase and reduces the expression of tyrosinase protein.[7] Studies have concluded that topical Silymarin has equal efficacy and better safety as compared to hydroquinone. So silymarin can be used as a more effective treatment option having fewer side effects for the treatment of melisma.[8]

Silymarin cream can be used in two different concentrations of 0.7% and 1.4% and this same study by Nofal et al proved that both concentrations as equally effective in terms of therapeutic response based on percent reduction in MASI score (39.21 vs. 33.84, p-value>0.05) with 0.7% and 1.4% concentrations of silymarin cream. Similarly, the relapse rate was very low, only 7.14% of the patients in both groups were identified to have relapse of melasma. This study also proved that the use of Silymarin cream in low concentration has equal efficacy making it more effective in terms of efficacy, cost, and adverse effects.[8]

Literature has proved the efficacy and advantages of Silymarin cream but research work on this treatment modality is limited especially in our population almost no study was found. So, this clinical trial study aims to compare Silymarin with first-line drug hydroquinone in terms of effectiveness and treatment response based on MASI score as well as relapse rate and patient satisfaction with treatment which will help in the identification of alternative treatment options for melasma with higher efficacy, less cost and higher compliance rate based on patient satisfaction.

Materials and Methods

This Randomized control trial was conducted at the dermatology outpatient department of Akbar Niazi Teaching Hospital, Bara Kahu, Islamabad, for a period of one year from April 2020 to April 2021. Permission was taken from the Institutional Review Board (IRB) before starting the study. All the females having aged more than 18 years with melasma of different severities, types and patterns were included in the study. Pregnant or lactating females, using hormonal birth control pills or any hormonal therapy, a history of using topical anti melasma therapy or topical steroids within 3 months were excluded from the study. Informed written consent was taken from the enrolled patients and confidentiality was maintained throughout the study.

A total of 112 patients consisting of two equal groups of 56 patients in each group were included in the study. WHO sample size calculator was used to determining the sample size using a Level of significance of 5%, Power of test of 80%, Population standard deviation of 20, Test value of the population mean value of percentage decrease in MASI score in Silymarin 0.7% group after 3 months 39.21 and 46.75 in Hydroquinone 4% group.[8]

Demographic information and details regarding onset and duration of disease, family history and any prior treatment, skin type, and pattern of melasma were

assessed. MASI scoring system was used to assess the severity of the melasma. The Melasma Area and Severity Index (MASI) is the most common outcome measure used for melasma studies, it ranges from 0 (none) to 3 (severe melasma) primarily based on intensity/type of pigmentation. All the patients in the study were divided into two groups randomly by lottery method. Group A was treated with silymarin 0.7% cream applied twice daily, and patients in group B were treated with 4% hydroquinone cream used daily once at night. Proper sun protection measures were advised to all patients. Use of Sunscreen (SPF ≥ 60) and use of physical protection like an umbrella or p-cap were advised use. Digital photography was used at baseline and every follow-up for three months.

All the patients were followed up for six months at monthly intervals. Patients in both groups got treatment for three months and were followed monthly for the next three months to record any relapse of melasma. The treatment response in both groups was measured by MASI score which was calculated at baseline and each follow-up visit for three months. Percent reduction in MASI score from baseline was used to assess the clinical efficacies of the treatments in both groups. The clinical efficacy was categorized based on percent reduction and > 75% reduction was taken as an excellent response, 50-75% reduction as a good response, 25-50% reduction as a medium response, and < 25% reduction as a poor response.[9]

Patient satisfaction was measured after six months by the Short Assessment of Patient Satisfaction (SAPS) and was graded as very unsatisfied (0–10), unsatisfied (11–18), satisfied (19–26), and very satisfied (27–28).[10] The treatment was considered safe if there was the absence of erythema and/or burning sensation associated with the treatment. Information was recorded on a specially designed proforma.

The data was analyzed with the help of Statistical Package for Social Sciences (SPSS) version 25. Data were presented as mean ± SD for quantitative variables and frequency with percentages for categorical variables. An independent sample t-test was used to compare mean MASI scores and percent decrease between both treatments groups at each follow-up. A Chi-square test was applied to compare the clinical efficacy and safety in terms of any side effects between both groups throughout the study period. A P-value of ≤0.05 was considered significant.

Results

The mean age of patients in Group A (Silymarin 0.7%) was 35.13 ± 3.87 years and in Group B (Hydroquinone 4%) was 34.16 ± 3.90 years. The mean duration of disease was noted to be 4.36 ± 1.65 years in Group A and 4.95 ± 1.89 in Group B. Family history of melasma was found in 14 (25%) patients in Group A and 8 (14.3%) patients in Group B. In Group A, 23 (41.1%) patients had sun exposure and 30 (53.6%) patients in Group B had sun exposure. The majority of the patients in both groups had an epidermal type of melasma (76.8% vs 62.5%) in Group A and Group B followed by the mixed type of melasma (14.3% vs 26.8%) in Group A and B respectively. In Group A, most of the patients 29 (51.8%) presented with mild severity of melasma followed by moderate severity in 25 (44.6%) patients. In Group B, the majority 32 (57.1%) of the patients had mild severity of melasma followed by 17 (30.4%) of the patients with moderate severity as elaborated in Table 1.

The mean MASI score at baseline in Silymarin 0.7% group was 18.77 ± 5.68 and in the hydroquinone 4% group it was 17.18 ± 6.29. There was no statistically significant (p-value < 0.05) difference between both groups after one month and two months of treatment based on MASI score. The mean MASI score after one month (13.32 ± 5.48 vs. 12.84 ± 4.78, p-value = 0.621) and two months (12.73 ± 5.17 vs. 11.09 ± 5.57, p-value = 0.109) in Silymarin 0.7% group and Hydroquinone 4% group respectively. The mean MASI score of the Hydroquinone 4% group (10.59 ± 5.74) was significantly (p-value < 0.05) less than the mean MASI score of the Silymarin 0.7% group (8.20 ± 4.41) after 3 months of treatment as shown in table 2.

There was no statistically significant (p-value > 0.05) difference in the therapeutic response of both drug groups after one month and two months of treatment. The therapeutic response became significantly better in Hydroquinone 4% group after three months of treatment showing higher proportions of medium (41.07% vs 28.57%) and excellent response (19.64% vs 7.14%) in the Hydroquinone 4% group as compared to the Silymarin 0.7% group as elaborated in Table 3.

According to the results of this study, adverse effects including erythema, burning, and scaling was detected in a large number of 34 (60.71%) patients treated with hydroquinone as compared to the Silymarin group in which only 7 (12.5%) patients complained about any adverse effect. Although a higher number of patients 11 (19.63%) in the hydroquinone group had recurrence as compared to 5 (8.93%) patients in the Silymarin

group had recurrence but this difference was not statistically significant (p-value > 0.05). Regarding patient satisfaction, it was noted that in Silymarin 0.7% treatment group greater patient satisfaction was observed as compared to the hydroquinone group, but this difference was also statistically insignificant (p-value > 0.05) as shown in table 4.

Table 1: Distribution of Demographic Characteristics of both groups

Characteristics	*Silymarin 0.7% Group A*		*Hydroquinone 4% Group B*		*P-value*
	Frequency	**Percentage**	**Frequency**	**Percentage**	
Age of the Patient (years)					
Mean ± SD	35.13 ± 3.87		34.16 ± 3.90		0.192
Duration of disease (years)					
Mean ± SD	4.36 ± 1.65		4.95 ± 1.89		0.08
Family History					
Yes	14	25.0	8	14.3	0.154
No	42	75.0	48	85.7	
Sun Exposure					
Yes	23	41.1	30	53.6	0.185
No	33	58.9	26	46.4	
Melasma Type					
Dermal	5	8.9	6	10.7	0.219
Epidermal	43	76.8	35	62.5	
Mixed	8	14.3	15	26.8	
Severity of Melasma					
Mild	29	51.8	32	57.1	0.108
Moderate	25	44.6	17	30.4	
Severe	2	3.6	7	12.5	
Total	**56**	**100**	**56**	**100**	

Table 2: Comparison of MASI Score between both groups

Silymarin 0.7%		*Hydroquinone 4%*		*P-value*
Mean	**Std. Deviation**	**Mean**	**Std. Deviation**	
MASI Score at baseline				
18.77	5.68	17.18	6.29	0.163
MASI Score after 1 month				
13.32	5.48	12.84	4.78	0.621
MASI Score after 2 months				
12.73	5.17	11.09	5.57	0.109
MASI Score after 3 months				
10.59	5.74	8.20	4.41	0.015

Table 3: Comparison of Therapeutic Response between both groups

Response	*Treatment Group*		*Total*	*P-value*
	Silymarin 0.7%	**Hydroquinone 4%**		
Therapeutic Response at 1 month				
Poor	32	35	67	0.414
Medium	17	18	35	
Good	7	3	10	
Therapeutic Response at 2 month				
Poor	27	30	57	0.126
Medium	24	14	38	
Good	4	9	13	
Excellent	1	3	4	
Therapeutic Response at 3 month				
Poor	14	10	24	0.043
Medium	16	23	39	
Good	22	12	34	
Excellent	4	11	15	
Total	**56**	**56**	**112**	

Table 4: Comparison of Adverse effects, recurrence rate, and Patient Satisfaction between both groups

	Treatment Group		*Total*	*P-value*
	Silymarin 0.7%	**Hydroquinone 4%**		
Adverse Effects				
Yes	7	34	41	0.000
No	49	22	71	
The recurrence rate at 6 months follow up				
Yes	5	11	16	0.105
No	51	45	96	
Patient Satisfaction				
Grade 0	5	3	8	0.133
Grade 1	13	8	21	
Grade 2	16	28	44	
Grade 3	22	17	39	
Total	**56**	**56**	**112**	

Discussion

Abnormal pigmentation of the skin cells is usually difficult to manage due to their ambiguous etiology or pathogenesis. It has been commonly observed that aging skin goes together with abnormal pigmentation. Some specific contributing factors can cause premature skin aging and pigmentation abnormalities. Some therapeutic modalities are effective for both. Melasma is a common hyperpigmentation disorder having a high relapsing rate. The psychological state of the affected patient is affected significantly by the negative impact of this disease. The exact etiology and pathogenesis of melasma are not yet clearly understood. However, oxidative stress due to ultraviolet rays has a significant role in the pathogenesis of melasma. Silymarin has an antioxidant effect and acts in different ways to reduce harmful effects of ultraviolet radiation including immune responses, inflammation, DNA damage, and pigmentation.[11]

Several skin disorders are considered to be associated with exposure to UV radiation. These disorders include sunburn cell formation, hyperplasia, erythema, edema, DNA damage, photoaging, melanogenesis, and skin cancers. It is established that reactive oxygen species (ROS) are induced by UV radiations, which result in oxidative stress in skin cells. This oxidative stress is the main cause of initiation, promotion, and progression of carcinogenesis and skin aging. Thus, the use of naturally occurring herbal compound based antioxidants is getting substantial attention to protect skin from the adverse effects of solar UV radiation.[12]

Studies have shown that melasma patients face strong psychosocial distress due to cosmetic disfigurement caused by the disease. Even though Hydroquinone has been regarded as a gold standard for the treatment of melasma, some other topical treatment options are available including Silymarin in the concentration of 0.7% and 1.4%. However, local application of any depigmentary agents may cause irritant dermatitis, exogenous ochronosis, and poor compliance.[13] The effects of solar ultraviolet radiation can be reduced and controlled by the antioxidant properties of Silymarin cream.[14]

The results of this present study showed that there was no statistically significant (p-value >0.05) difference in efficacy between both groups after one and two months of treatment based on MASI score. The mean MASI score after one month was recorded as (13.32 ± 5.48 vs. 12.84 ± 4.78, p-value = 0.621) and two months (12.73 ± 5.17 vs. 11.09 ± 5.57, p-value = 0.109) in Silymarin 0.7% group and Hydroquinone 4% group respectively. The mean MASI score of the Hydroquinone 4% group (10.59 ± 5.74) was significantly (p-value < 0.05) less than the mean MASI score of the Silymarin 0.7% group (8.20 ± 4.41) after 3 months of treatment. Both groups showed a significant efficacy that is a decrease in mean MASI score in the first two months of treatment from baseline [15,16] and there was no significant difference in comparative efficacy of both groups, revealing a similar efficacy of both groups. Parallel results were recorded in other studies in the literature comparing Silymarin and hydroquinone drugs with other treatment modalities used for melisma.[17]

Silymarin can be considered more effective because of its ability to reduce and conquer the adverse effects of solar UV radiation. It is effective on all complications associated with UV radiation like oxidative stress, edema, inflammation, and DNA damage.[18] Silymarin acts as a strong antioxidant to help protect skin cells from the harmful effects of solar UV radiation. It provides significant protection from the depletion of catalase activity caused by UVB. Damaging biochemical reactions can be terminated by reducing free radicals and reactive oxygen species and this can be done effectively through silymarin cream, which also helps in strengthening of antioxidant status of skin cells.[19]

Hydroquinone is also an effective treatment for melasma proved by many studies. The results from this clinical trial also support the effectiveness of hydroquinone showing similar treatment responses for both treatments silymarin and hydroquinone. But the

use of hydroquinone is associated with some adverse effects which were not found in patients treated with silymarin so it can be used as a promising alternative to hydroquinone.[20]

According to the results of this present study adverse effects including erythema, burning, and scaling were detected in a large number of 60.71% vs. 12.5% of patients treated with hydroquinone as compared to Silymarin. There was no statistically significant (P-value > 0.05) difference in hydroquinone and Silymarin groups based on recurrence rate. Regarding patient satisfaction, it was noted that in Silymarin 0.7% treatment group higher proportions of higher-grade patient satisfaction were observed as compared to the hydroquinone group, but this difference was also statistically insignificant (p-value > 0.05). These results came in agreement with previous studies, which reported almost no adverse effects during treatment of melasma by silymarin and a higher number of adverse effects associated with hydroquinone.[17,21]

Conclusion

The results of this present study concluded that topical silymarin has equal efficacy for the treatment of melasma with comparatively very lesser adverse effects as compared to hydroquinone. There was no difference in recurrence rate and patient satisfaction with both treatment modalities. So, Silymarin can be recommended as a promising alternative to conventional hydroquinone. Further better results can be achieved with a longer duration of therapy.

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