

Original Article

Comparison of efficacy of topical 2% liquiritin, topical 4% liquiritin and topical 4% hydroquinone in the management of melasma

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Abstract *Background* Melasma is an acquired irregular brownish hyperpigmentation of face and occasionally neck with a poorly understood etiology. Hydroquinone-based formulations remain the mainstay of treatment.

Objectives To compare the efficacy of topical 2% liquiritin, topical 4% liquiritin and topical 4% hydroquinone for management of melasma.

Patients and methods 90 patients of melasma coming through out-patient department of Nishtar Hospital, Multan, Pakistan between January, 2007 to July, 2007 were enrolled. Detailed history and clinical examination were entered in the pro forma. Patients were divided into three groups (A, B and C). Group A was treated with 4% hydroquinone, group B with 4% liquiritin and group C with 2% liquiritin for 8 weeks. Patients were followed up for another 4 weeks and efficacy was assessed at week 16 by change in the intensity of pigmentation, size of melasma and improvement in photographic appearance.

Results Study included 90 patients between ages 18-40 years. There were 3 males and 87 females. Patients had melasma for an average of 5.80 years. 68 were married and 22 were unmarried. Clinical examination showed that 50 patients had centrofacial distribution, 35 had malar distribution and 5 had mandibular pattern. In group A (4% hydroquinone) 22 (73.3%) patients improved, 5 patients (16.7%) had no change and 3 patients (10%) deteriorated. In group B (4% liquiritin), 29 patients (96.7%) improved, one patient (3.3%) had no change. In group C (patients using 2% liquiritin) 26 patients (86.7%) improved and 4 patients (13.3%) had no significant improvement. None of the patients developed any complication.

Conclusion Topical 4% liquiritin is significantly more effective than topical 2% liquiritin and topical 2% liquiritin is also significantly more effective than 4% hydroquinone.

Key words

Melasma, pigmentation disorders, skin diseases.

Introduction

Melasma is an asymmetrical brown or greyish-brown facial hypermelanosis, often affecting women, especially those living in areas of intense sunlight exposure. The precise cause of melasma remains unknown; however, there are many possible contributing factors.¹ Natural and synthetic estrogens and

progesterone hormones have been incriminated in pathogenesis due to the association of the disease with pregnancy, oral contraceptives and ovarian tumor. Sunlight, genetic factors, thyroid dysfunction, and cosmetics, phototoxic and antiseizure drugs have also been implicated as other etiological factors.²

Melasma can be both dermal and epidermal. Dermal melasma is resistant to treatment and has tendency to relapse. As melasma is one of the commonest aesthetically harrowing entity, its proper treatment and cure is mandatory.

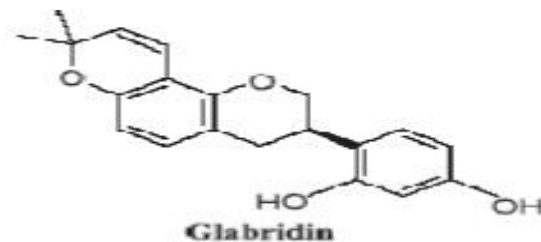
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The mainstay of treatment remains topical depigmenting agents. Hydroquinone (HQ) is most commonly used. It is a hydroxyphenolic chemical that inhibits tyrosinase, leading to the decreased production of melanin.³ Concentrations vary from 2% to 4% and even higher. Another lightening agent is retinoic acid (tretinoin). The retinoid is believed to work by increasing keratinocyte turnover and thus limiting the transfer of melanosomes to keratinocytes.⁴ Azelaic acid, available as a 20% cream-based formulation, appears to be as effective as 4% HQ and superior to 2% HQ in the treatment of melasma. The mechanism of action is not fully understood. DNA synthesis is reduced probably.⁵ Combination therapies such as hydroquinone, tretinoin, and corticosteroids have been used in the treatment of melasma, and are thought to increase efficacy.⁶

Chemical peels are relatively new treatments. Superficial and medium-depth chemical peels have become an effective procedure in management of melasma.⁷ Laser treatments and intense pulsed light therapy are additional therapeutic modalities that have been used to treat melasma. The use of broad-spectrum (UVA + UVB) sunscreen is important and it should never be ignored during any of treatment protocol.⁸ Kojic acid, isopropylcatechol, N-acetyl-4-cysteaminylphenol, and certain natural extracts like arbutin, soy and many others are being investigated for their ability to produce depigmentation, but their efficacy, safety, or trial design indicates that the interventions need further study before they could be recommended.⁹

Glycyrrhiza glabra is the Latin name of plant liquorice.¹⁰ The word 'liquorice' is derived from the ancient Greek words meaning sweet root. Liquorice root is being used in many traditional medicines since centuries. It has several active ingredients like saponins,



flavonoids, isoflavones, coumarins and stilbenoids. Saponins are glycyrrhizic acid, liquiritic acid and licorice acid. They are mainly responsible for the sweet taste of the liquorice. They have anti-inflammatory properties.¹¹ Flavonoids give yellow colour to liquorice. Its active ingredients are liquiritin and liquiritigenin. Its main ingredient is glabridin which is an effective tyrosinase inhibitor and acts as bleaching agent. Glabridin decreases specifically the activities of T1 and T3 tyrosinase isozymes.¹² It has been used in many skin lightning cosmetics. Much has been written about depigmentation effect of liquiritin but still clinical studies regarding its efficacy in melasma are limited.

Patients and methods

It was a double-blind clinical trial (interventional study).

Sample selection

Ninety patients of melasma coming through out-patient department of Nishtar Hospital, Multan, Pakistan were included in this study. All patients were randomized into three groups "A", "B" and "C". Non-probability purposive sampling was done. Each group had thirty patients. Group A was treated with 4% hydroquinone, group B with 4% liquiritin and group C with 2% liquiritin.

Patients aged 18-40 years with epidermal melasma without any other skin disease were included in this study. Patients who were pregnant, hypertensive, suffering from renal disease or taking any oral drug was excluded.

Treatment protocol

All patients were diagnosed for melasma by history, clinical examination and Wood's light examination. Patients were assessed by following 3 parameters.

- A. Intensity of melasma was rated by the 4-points scale in relation to patient's normal facial skin: grade 0: clear (no pigmentation); grade I: mildly pigmented; grade II: moderately pigmented; and grade III: severely pigmented.
- B. The size of lesion was measured directly using a millimeter grid scale. Sizes were taken in both horizontal and vertical directions.
- C. Photographs of only those patients who allowed candidly were taken.

Liquiritin was obtained from a licensed pharmacy in Multan. 4% liquiritin cream was prepared by mixing 4 ml of liquiritin with 96 grams of cream. 2% liquiritin cream was prepared by mixing 2 ml of liquiritin with 98 grams of cream. All drugs were packed in 30 gram plastic containers and labeled in such a manner that patients could not know which drug they were using.

Patients in group A applied 4 % hydroquinone once daily at night for eight weeks. Group B was given 4% liquiritin cream to apply once daily at night for eight weeks and group C was given 2% liquiritin cream to apply once daily at night. They were given all necessary instructions about applications and use of sun block during day.

Patients were assessed after four weeks and another 30 gram plastic container was given for the next 4 weeks. They were asked for any side effects at each visit. Patients were examined after eight week for final results through out-patient department. Post treatment

photographs were taken after eight weeks of treatment.

Efficacy was measured by three parameters i.e. change in photograph, decrease in intensity of pigmentation and decrease in size of lesion. Each parameter was categorized as improved, not improved and deteriorated. Assessment of the photographs was done by four different persons, who were unaware of the treatment modalities.

Statistical analysis

Data collection tool was a proforma. Variables were entered on SPSS version 10.0. One-way analysis of variance (ANOVA) was used to find out comparisons of treatments between groups. P value of <0.05 was considered statistically significant.

Results

This study enrolled 90 patients of melasma between ages of 18 to 40 years. Mean age of these patients were 29.31 ± 6.47 years. There were 3 (3.3%) males and 87 (96.7%) females. Patients had melasma for an average of 5.80 ± 3.93 years (range was 1-17 years). History showed that 68 (75.6%) were married and 22 (24.4%) were unmarried. The clinical examination showed that 50 (55.6%) had centrofacial distribution, 35 (38.9%) had malar and 5(5.6%) had mandibular pattern.

Table 1 shows the change in intensity of colour before and after treatment whereas **Table 2** depicts the results in terms of change in photographic appearance, change in size and pigmentation in three groups.

Overall efficacy shoed that in group A, 22 patients (73.3 %) improved, 5 patients (16.7%) had no change and 3 patients (10%) deteriorated. All 3 deteriorated patients had increased pigmentation. In group B, 29 patients (96.7%) improved and one patient

Table 1 Change in intensity of pigmentation.

Intensity of pigmentation	Before treatment			After treatment		
	Group A	Group B	Group C	Group A	Group B	Group C
Clear	-	-	-	2	4	4
Grade 1	12	9	10	18	21	19
Grade ii	7	11	7	7	4	5
Grade iii	10	10	13	3	1	2
Total	30	30	30	30	30	30

Table 2 Results after eight weeks.

Parameters	Category	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Change in photograph	Improved	22 (73.3%)	29 (96.8%)	26 (86.7%)	P=0.02
	Not improved	5 (16.7%)	1 (3.3%)	4 (13.3%)	
	Deteriorated	3 (10%)	-	-	
Change in size	Improved	19 (63.3%)	25 (83.3%)	23 (76.7%)	P=0.01
	Not improved	10 (33.3%)	5 (16.7%)	7 (23.3%)	
	Deteriorated	1 (3.3%)	-	-	
Change in pigmentation	Improved	21 (70%)	28 (93.3%)	24-80%)	P=0.04
	Not improved	6 (20%)	2 (6.7%)	6-20%)	
	Deteriorated	3 (10%)	-	-	
Net result	Improved	22 (73.3%)	29 (96.7%)	26 (86.7%)	P=0.02
	Not improved	5 (16.7%)	1 (3.3%)	4 (13.3%)	
	Deteriorated	3 (10%)	-	-	



Figure 1 Before using 4% liquiritin.



Figure 2 After using 4% liquiritin.

(3.3%) had no change. In group C, 26 patients (86.7%) improved and 4 patients had no change (13.3%), **Figures 1 and 2**. One way ANOVA (analysis of variance) was applied to compare change in photographs among groups. P value between groups was <0.05. In terms of change in intensity of pigmentation, in group A 21 (70%) patients improved, 6 (20%) patients had no change and 3 (10%) patients deteriorated; in group B, 28 (93.3%) patients

improved, 2 (6.7%) patients had no change; and in group C, 24 (80%) patients improved and 6 (20%) patients had no change (change in intensity of pigmentation (P<0.05). Assessment of change in size of melasma was as follows: in group A, 19 (63.3%) patients improved, 10 (33.3%) patients had no change and one (3.3%) patient deteriorated; in group B, 25 (83.3%) patients improved and 5

(16.7%) patients had no change; and in group C, 23 (76.7%) patients improved and 7 patients (23.3%) had no change ($P < 0.05$).

No major side effect was seen in either group except 3 patients in group A, 2 developed contact dermatitis and one hyperpigmentation after the use of 4% hydroquinone use.

Discussion

Melasma is a pattern of pigmentation seen mainly in women, though in Asia it is frequently seen in men, as well. It is more prevalent in South Asian countries due to darker complexion (skin type IV to V) and increased ultraviolet radiations. As most of the females are uneducated and poor so they are unaware of the importance of sun avoidance which further increases their probability of having melasma. Treating this condition is challenging and core of its treatment has always been hydroquinone based formulations. Another problem with high concentration of hydroquinone is contact dermatitis. Although various other treatments are also available but all are very costly and results are delayed.

The main purpose of this study was to compare efficacy of herbal treatment with a standard options in treatment of melasma. This is a unique study of its kind, as up till now hydroquinone has never been compared with liquiritin. Scanty national and international data are available regarding treatment of melasma with different concentrations of liquiritin.

In the present study, 73.3% patients in group A had significant improvement whereas 96.7% patients in group B showed improvement and 86.7% patients in group C exhibited improvement. Statistically significant difference was observed in group B over group C and A. There was no major side effect noticed in group B and C. However three

patients in 4% hydroquinone group (group A) deteriorated. Two of them developed contact dermatitis and one patient developed hyperpigmentation.

Our results are similar to those by Amir and Metwalli from Egypt.¹³ They treated 20 patients of melasma with 2% liquiritin cream for 10 weeks. Good to excellent results were seen in 18 out of 20 (90%) patients.

In our study, 4% liquiritin showed significantly better results than 2% liquiritin and 4% hydroquinone. Its effect was better ahead than other treatments in all aspects. However, maximum benefit was noticed in improving intensity and cosmetic appearance. Effect on size was delayed but was still better than other two groups. With 4% liquiritin and 2% liquiritin visible difference was evident in four weeks as compared to 4% hydroquinone in which difference was noticed in eight weeks.

As melasma consists of zones of asymmetrical hyperpigmentation its improvement also results in uneven lightening of the skin. Another effect of 4% liquiritin is that it resulted in more even depigmentation than 4% hydroquinone.

As far as the psychological effects of treatment were concerned, patient satisfaction was more with 4% liquiritin because colour and smell of the cream was different then the ordinary depigmentation creams. 2% liquiritin also had same smell but much lighter colour. Most of the patients with 4% hydroquinone were reluctant to use cream as they thought that they have used the same type of cream earlier.

Another worth mentioning fact was that the colour and smell of both liquiritin containing creams did not change during the treatment. Most of the 4% hydroquinone cream changed its colour due to oxidation with air. So they

had to be replaced by the new creams which increased the expenses of the study.

Topical effect of liquiritin is due to its tendency to reduce UVB erythema, anti-inflammatory effect and above all inhibitory effect on melanosomes. Combination of all these properties has made it even superior to the triple therapy (combination of hydroquinone, tretinoin, and corticosteroids). Yokota *et al.* in Japan worked on inhibitory effect of glabridin (liquorice extract) on murine melanoma cells and guinea pig skins. They not only proved the inhibitory effect of glabridin on melanogenesis but also showed that UVB-induced pigmentation and erythema in the skins of guinea pigs were inhibited by topical applications of glabridin. An anti-inflammatory effect of glabridin *in vitro* was due to its inhibition of superoxide anion productions and cyclooxygenase activities.¹⁴

The main limitation of this study was illiteracy. It was difficult to explain the importance of sun block. Significant number of patients during follows up visits admitted non compliance of sun block cream during day time. This can affect the results.

Conclusion

In countries like Pakistan where sun exposure is intense the probability of developing melasma is higher. Instead of expensive treatments, there is a need to try natural remedies which are cheaper and effective. Liquiritin, therefore, offers locally relevant and affordable solution to the problem. In future, topical liquiritin should be combined with hydroquinone, tretinoin or kojic acid to yield more impressive results.

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