Efficacy and safety of azelaic acid 20% plus hydroquinone 5% in the management of melasma

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Background: Melasma is a brown or grayish brown symmetrical facial hyperpigmentation.A number of medicamens can be used for the treatment of this condition. For better results in treating melasma, combination therapy is preferred. The aim of this study was to determine the clinical efficacy and adverse effects of azelaic acid 20% plus hydroquinone 5% versus hydroquinone 5% alone in the management of melasma.

Method: This study was performed as a double blind randomized clinical trial. We randomly prescribed two regimes including azelaic acid 20% cream plus hydroquinone 5% or hydroquinone 5% alone once daily for 4 months in 64 patients. Clinical efficacy (with MASI score) and side effects were assessed after one, two and four months of treatment.

Result: MASI score reduction was from 9.35 to 2.9 in patients using azelaic acid 20% plus hydroquinone and from 9.58 to 4.02 in patients using hydroquinone 5%. Drug adverse effects, including burning (most frequent), itching, stinging, dryness and erythema, were present in 50% of the participants in the azelaic acid 20% plus hydroquinone group and 35% of the individuals in the hydroquinone 5% group (P= 0.034), but were tolerated by most patients.

Conclusion: Both therapeutic regimens showed a remarkable efficacy in the treatment of melasma but azelaic acid 20% plus hydroquinone was more effective with a more rapid onset of therapeutic response. Azelaic acid 20% plus hydroquinone had more side effects although they were slight in most cases.

Keywords: azelaic acid, hydroquinone, melasma, treatment

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INTRODUCTION

Melasma, a brown or grayish brown symmetrical facial hyperpigmentation, is primarily a disease of childbearing women, with men representing only 10% of the cases [1]. Although its etiology is unknown, UV light, pregnancy, thyroid disturbances and medications (i.e. OCP and anti epileptics) have all been implicated in its pathogenesis [2]. Furthermore, there appears to be genetic and ethnic components, as it often runs in families and its prevalence is higher in individuals with fitzpatrik skin type 4-6 [3]. Melanocyte hyperactivity and proliferation is found in melasma [4,5]; increased melanin production results in excessive melanin deposition in keratinocytes of the epidermis or in macrophages of the dermis or both [5].

The pattern of deposition is thus characterized as epidermal, dermal or mixed [4]. Epidermal melasma has a better prognosis. There is no direct effective therapy for dermal pigmentation. Drugs inhibit epidermal melanogenesis. If melanogenesis is

inhibited for a long period, dermal pigmentation slowly resolves [6,7].

For better results in treating melasma, combination therapy is preferred [8]. Hence, in this study, we evaluated the synergistic effect of azelaic acid 20% and hydroquinone 5% on melasma in comparison with hydroquinone 5% alone.

PATIENTS AND METHODS

This multicenter randomized double blind clinical trial was conducted to compare the efficacy and complications of azelaic acid 20% plus hydroquinone 5% solution (AZA+HQ) and hydroquinone 5% (HQ) solution in patients who attended dermatology clinics of Azad University from 2009 to 2010.

Study Population

The study included 64 adult female patients with Fitzpatrick skin type 1 to 4. The patients were clinically diagnosed with mild or moderate melasma. These patients divided to equal groups each with 32 melasma patients.

Patients were excluded from the study if they had used any topical hypopigmenting preparation within the last 6 months or had administered systemic corticostroids or OCP.

Study medication and protocol

Formula that we used in this study was hydroquinone 5% + azelaic acid 20% in base of etanol 70° in one group and hydroquinone 5% in base etanol 70° in the other group. Propylenglycol 15% was used in both products to enhance penetration. We also used ascorbic acid 5% as an antioxidant in both formulations.

The study medication was applied once in the evening after washing the face. It was mandatory to wear sunscreen in the morning. In the baseline visit, the area, darkness and homogenicity of the lesion was measured and photographs were taken from patients, also history of the patient's age, skin type and location of melasma was taken.

At follow-up visits at weeks 4, 8 and 16, the physician carried out a global assessment including area, darkness and homogeneity of the lesion and also photographs were taken from patients. The measured area, darkness and homogeneity were treated with the MASI score formula which is as follows:

MASI: forehead 30% (D+H)A + Right malar 30% (D+H)A + Left malar 30% (D+H)A+ Chin 10%(D+H)A. Table 1 shows the scores of area, darkness and homogeneity using for melasma severity.

The physicians also measured safety variables, the signs comprised oiliness, dryness, erythema and peeling and the symptoms comprised burning and stinging.

According to table 2 complications of the two regimes in the end of first, second and fourth month of treatment was measured by the physicians. The safety variables were scored from 0-5 according to their severity by the physician.

The collected data were analyzed with SPSS software using independent t-test. This study was

Table 1. Melasma Area Severity Index (MASI)

Area	Darkness	Homogeneity
0 → No involvement	0 → Normal skin with out pigmentation	0 → Normal skin color without evidence of hyperpigmentation
1 → ≤ 10 %	1 → Barely visible hyperpigmentation	1 → Specks of involvement
2 → 10-29 %	2 → Mild hyperpigmentation	2 → Small patch areas of involvement <1.5cm diameter
3 → 30-49 %	3 → Moderate hyperpigmentation	3 → Patches of involvement >2cm
4 → 50-69 %	4 → Severe hyperpigmentation	4 → Uniform skin without any clear areas
5 → 70-89 %		
6 → 90-100 %		

Table 2. Scales for safety variables

Variable	Value	Description
Oiliness, dryness	0	Normal
Erythema, and peeling	1	Trace, localized
	2	Mild, diffuse
	3	Moderate, diffuse
	4	Marked, dense
	5	Severe, prominent and dense
Burning and stinging	0	Normal, no discomfort
	1	Trace, awareness without discomfort
	2	Mild, noticeable discomfort causing intermittent awareness
	3	Moderate, Mild, noticeable discomfort causing continuous awareness
	4	Marked, definite discomfort that occasionally interferes with normal daily activities
	5	Severe, continuous discomfort that interferes with normal daily activities

approved by the ethics committee of our university and was performed according to the Declaration of Helsinki Principles. All of the participants were instructed about the study and they signed the informed consent forms.

RESULTS

The mean age of the participants in the AZA+HQ and HQ groups was 35.5 and 32.4 years respectively and Fitzpatrick skin type was four in 62.5% and 53.3% of the participants in the AZA+HQ and HQ groups, respectively. Prior administration of OCP was found in 43.8% of the individuals in the AZA+HQ group and 33.3% of the participants in the HQ group. Multiple lesions were seen in 18.8% and 26.7% of the individuals in AZA+HQ and HQ groups, respectively.

One hundred percent (32/32) of the participants in the AZA+HQ group and 93.75% (30/32) of the individuals in the HQ group showed reduction in MASI score after two months and one hundred percent (32/32) in the AZA+HQ group and 87.5% (28/32) in the HQ group had reduction in MASI score after four months.

Table 3 shows the mean MASI score before treatment and after one, two and four months in the two groups. Both groups showed a significant decrease in pigmentation (P<0.05). There was a 11% difference in mean MASI score reduction after four months between two groups, which was statistically significant (P<0.05).

Table 3. Mean MASI score before treatment and after one, two and four months in the two groups.

Duration of treatment	Az 20%+HQ 5% mean MASI	HQ 5% Mean MASI
Before treatment	9.35	9.58
4 weeks	8.1	8.7
8 weeks	5.7	6.3
16 weeks	2.9	4.02

Adverse effects

During the treatment symptoms (burning and stinging) were seen in 13 (50%) cases in the AZA+HQ group. The severity score was less than 4 in 10 (80%) cases and 5 in 3 (20%) cases and signs (dryness, erythema, peeling) were seen in 7 (26%) cases. The severity score was less than 4 in 4 (57%) patients and 5 in 3 (43%) cases.During the treatment in the HQ group, symptoms were seen in 8 (35%) individuals and the severity score was less than 4 in all cases. Signs were seen in 3 (15%) cases and the severity score was less than 4 in all individuals. There was no significant difference regarding the presence of side-effects between two groups (P=0.034).

DISCUSSION

The purpose of the study was to evaluate the effect of the combination of azelaic acid 20% plus hydroquinone 5% in the treatment of melasma. According to the results, azelaic acid 20% plus HQ 5% was significantly more effective than HQ 5% in the treatment of melasma. This is possibly due to the additive effect of azelaic acid on hydroquinone in inhibition of melanogenesis. Hydroquinone is a hydroxyphenolic chemical that inhibits the conversion of dopa to melanin by inhibiting tyrosinase, increasing the degradation of melanosomes and inhibiting DNA and RNA synthesis of melanocytes [8,9]. It is the most important agent in the treatment of melasma and

is used in concentrations of 2-10% [10]; its efficacy and complications are directly related to the concentration of the drug [11].

Azelaic acid is a non-phenolic bleaching agent. It is believed that azelaic acid decreases hyperpigmentation by inhibiting tyrosinase. It also attenuates free radical production, a contributing factor in hyperpigmentation [9,10]. The results of our study provides evidence for other studies that combination therapy has better results in treating melasma [11,12], but previous studies did not measure the efficacy of azelaic acid plus HQ in the treatment of melasma.

According to this study, both therapeutic regimens showed a considerable efficacy in treatment of melasma but AZA+HQ were more effective with a more rapid onset of therapeutic response. AZA+HQ had more side effects although they were slight in most patients. Further studies with larger sample size could be more beneficial to elucidate the efficacy and safety of azelaic acid in the treatment of melasma.

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