Original Contribution

Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma

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Summary

Background Melasma is an irregular brown or grayish-brown symmetric facial hypermelanosis, often affecting women, especially those living in areas with intense ultraviolet radiation.

Objective Comparison of therapeutic effects of 20% azelaic acid and 4% hydroquinone cream in the treatment of melasma.

Methods Twenty-nine women with melasma were recruited. Fifteen patients were treated with 4% hydroquinone cream and 14 patients were treated with azelaic acid cream for 2 months. The cream was applied twice daily. A broad-spectrum sunscreen was used concomitantly by both groups. The Melasma Area Severity Index (MASI) scores were determined prior to treatment and at each follow-up.

Results The mean MASI score before treatment was 7.2 ± 3.2 in the hydroquinone group and 7.6 ± 3.5 in the azelaic acid group, with no significant difference between them (*t*-test, CI 95% = −2.9 to 2.2). One month after treatment, the mean MASI score reached 6.7 ± 3.4 with hydroquinone and 6.3 ± 3.4 with azelaic acid with no significant difference between them (*t*-test, CI 95% = −2.2 to 3). After 2 months' treatment, the MASI score was 6.2 ± 3.6 with hydroquinone and 3.8 ± 2.8 with azelaic acid, a significant statistical difference (*t*-test, CI 95% = 0.03–4.9).

Conclusions In conclusion, this study suggests that 20% azelaic acid cream applied twice daily may be more effective than hydroquinone 4% in reducing mild melasma. However, because this was an open trial, it is suggested that further studies involving large groups of patients be conducted to achieve a more conclusive result.

Keywords: azelaic acid, hydroquinone, melasma

Introduction

Melasma is a common acquired, chronic, recurrent, symmetric hypermelanosis characterized by irregular light to gray-brown macules and patches with well-defined margins on sun exposed areas of the body.[1–4] Melasma is more common in women, who account for 90% of all cases, and appears in all racial types, but it is particularly prevalent in those with skin types IV to VI who live in areas of high ultraviolet radiation.[2,5,6]

Etiologic factors in the pathogenesis of melasma include genetic influences, exposure to UV radiation, pregnancy, hormonal therapies (including oral contraceptives (OCP) and thyroid hormones), cosmetics, phototoxic drugs, and antiseizure medications.[1,2,7–9] Melasma has been attributed to an elevation of melamocyte-stimulating hormone, estrogen, and progesterone leading to increased melanogenesis.[10] The actual pathogenicity of melasma is not yet fully understood.[3,11] Various factors and causes are responsible for the pathogenesis of melasma, but a genetic

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predisposition and solar radiation (UV radiation and visible light) may be the two most important factors.[4]

Melasma is divided into three types based on Wood's lamp examination of the skin. The epidermal type exhibits increased melanin predominantly in the basal and suprabasal epidermis with accentuation by Wood's lamp. The best therapeutic results are normally achieved in epidermal melasma.[1]

The most commonly used treatment for all types of hyperpigmentary disorders is topical hydroquinone. It is one of the most effective inhibitors of melanogenesis *in vitro* and *in vivo*.[12] Hydroquinone has well-established efficacy against hyperpigmentation but can also lighten normally pigmented skin,[13] and repeated application of hydroquinone can cause leukoderma or vitiligo-like hypochromia[14] and occasionally causes toxic reactions. Thus, it is necessary to develop a more effective and less irritating alternative treatment for better management of melasma.

Azelaic acid is a naturally occurring saturated dicarboxylic acid and has antiproliferative and cytotoxic effects on a variety of tumoral cells in culture, which are mediated via inhibition of mitochondrial oxidoreductase activity and DNA synthesis, rather than via inhibition of tyrosinase activity, but normal cells remain practically unaffected.[5,11,15,16] Azelaic acid appears to act selectively on hyperactive and abnormal melanocytes.[15]

To investigate the clinical efficacy of azelaic acid in the treatment of melasma, this clinical trial of 29 patients was undertaken in a dermatology center.

Patients and methods

The present study is an open label clinical trial carried out over a period of 2 months. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of Iran University of Medical Sciences. Informed consent was obtained from all patients before recruitment. Women with melasma were chosen from the dermatology clinic of Hazrat Rasoul Hospital, Iran University of Medical Sciences.

The inclusion criteria required a diagnosis of epidermal melasma confirmed by Wood's lamp examination of more than 6 months duration. All patients had been without any treatment at least 2 months before the study.

Patients were excluded from the study if they were receiving OCP or corticosteroid therapy or if they had a history of endocrine disorders. Pregnant and lactating women were excluded from the study.

At the initial visit, patients' medical histories were taken, stressing the time of onset, history of pregnancy, contraceptive pill use, sun exposure, drug history, and other influencing or exacerbating factors, and their melasma type was assessed by Wood's lamp.

A clinical pattern of melasma was assigned to each patient: centrofacial, malar, or mandibular. Wood's lamp was used to determine the melasma type as epidermal, dermal, or mixed, and only the epidermal types were included in the study.

Patients were then randomized to receive either azelaic acid 20% or hydroquinone 4% cream. Patients applied the medication twice daily for 8 weeks. All patients also applied a broad-spectrum standardized sunscreen to their entire face and repeated it every 3 h.

Clinical assessment

Clinical evaluations were performed by the investigators at month one and at the end of the study. The evaluators were blinded to the study medication. Color facial photographs were taken at the beginning, after 1 month, and at the end of the study.

Evaluation of Melasma Area Severity Index (MASI) scores was performed at baseline, at month one and at the end of the study.

The MASI score is an index used to quantify the severity of melasma and changes during therapy. The MASI is a reliable measure of the severity of melasma.[17] According to the MASI score, the face is divided into four areas: forehead (F), right malar (RM), left malar (LM), and chin (C), which correspond to 30%, 30%, 30%, and 10% of the total face area, respectively. The melasma in each of these areas was graded on three variables: percentage of total area involved in each of these was given a numerical value of 0–6: 0 (no involvement), (1) 0–9%, (2) 10–29%, (3) 30–49, (4) 50–69, (5) 70–89, and (6) 90–100%. Other parameters were darkness (D), measured on a scale of 0 (absent) to 4 (maximum), and homogeneity, on a scale of 0 (absent) to 4 (maximum). The MASI was then calculated by the following equation according to the formulation of Kimbrough-Green *et al.*:[18]

$$\mathrm{MASI} = 0.3(\mathrm{D_F} + \mathrm{H_F})\mathrm{A_F} + 0.3(\mathrm{D_{RM}} + \mathrm{H_{RM}})\mathrm{A_{RM}} + 0.3(\mathrm{D_{LM}} + \mathrm{H_{LM}})\mathrm{A_{LM}} + 0.1(\mathrm{D_C} + \mathrm{H_C})\mathrm{A_C}$$

where D is darkness, H is homogeneity, A is area, F is forehead, RM is right malar, LM is left malar, C is chin, and the values 0.3, 0.3, 0.3, and 0.1 are respective percentages of total facial area. Recently, a new modified MASI score was developed by Pandya *et al.* in which the

homogeneity was omitted from the formula.[17] A mean of the MASI scores (original method) by each investigator was calculated.

The clinical assessment was grouped into four categories: (i) no effect (no visible changes of pigmentation); (ii) mild (decrease of visible pigmentation, but there is still some visible border); (iii) moderate (marked decrease of visible pigmentation, but there is still some visible border); and (iv) excellent (a complete loss of visible abnormal pigmentation), which was developed by Lee *et al.*[4] This was a modification of the objective assessment developed by Jimbow.[19]

Patients rated the severity of skin redness (erythema), dryness, itching, burning, irritation and hyperpigmentation on a scale of 0 (= none) to 4 (= severe). Erythema, dryness, and other objective side effects were also rated by the investigators.

Statistical analysis

Sample size was calculated by the formula below, in which α was equal to 0.05 and β was equal to 0.2 (power in this study was 80%):

$$n = \frac{2(z_{1-\alpha} + z_{1-\beta})^2 P(1-P)}{(P_1 - P_2)^2}$$

$P = 0.625$, the calculated sample size was 15 in each group. Convenience sampling method was used.

A *P*-value of 0.05 or less was considered to indicate significance. All analyses were performed with the use of SPSS (statistical package for social sciences) software (version 16), Chicago, IL, USA. For the comparison of MASI scores in each drug group, an independent *t*-test was used. Normality was tested with a Kolmogorov–Smirnov test. The grades in objective assessment were compared with the Mann–Whitney test.

Results

A total of 40 patients with melasma were evaluated for inclusion, 30 of which met the inclusion criteria and were enrolled in the study. One patient in the azelaic acid group discontinued her treatment after 2 weeks, and so the results are based on the 29 patients who continued the trial. Fifteen patients (51.7%) were treated with hydroquinone, and 14 patients (47.3%) were treated with azelaic acid, and all of them completed the study. All women had epidermal type of melasma: 21 (72.4%) had centrofacial type, 7 (24.1%) had malar type, and one (3.4%) had mandibular type. The mean age of the studied patients was 34.6 years (34.6 ± 6.6) (mean ± SD), and mean duration of the disease was 4.1 years (4.1 ± 2.9). Twenty (69%) patients had a history of OCP use.

The mean of MASI score before therapy was 7.4 (7.4 ± 3.3). Mean MASI score after 1 month of treatment was 6.5 (6.5 ± 3.3) and after 2 months was 5.04 (5.04 ± 3.4). The decrease in MASI scores after 1 and 2 months' therapy was statistically significant (paired *t*-test, $P < 0.001$). Before treatment, the mean MASI score was 7.2 ± 3.2 in hydroquinone group and 7.6 ± 3.5 in the azelaic acid group, with no significant difference being found between them (*t*-test, CI 95% = −2.9 to 2.2). The mean MASI score reached 6.7 ± 3.4 after 1 month of treatment with hydroquinone and 6.3 ± 3.4 after treatment with azelaic acid, with no significant difference noted between them (*t*-test, CI 95% = −2.2 to 3). After 2 months' treatment, the MASI score was 6.2 ± 3.6 with hydroquinone and 3.8 ± 2.8 with azelaic acid. This showed a significant statistical difference (*t*-test, CI 95% = 0.03–4.9). Figure 1 shows error bars of the two drugs' effectiveness during the first and second months.

Table 1 shows the objective assessment of pigmentary responses in both hydroquinone and azelaic acid groups.

Comparison of the pigmentary response in these two drug groups showed a significant difference (Mann–Whitney, $P = 0.05$) only in the second follow-up period. A good clinical response in one patient treated with azelaic acid and in one with hydroquinone is shown in Figure 2.

Adverse effects in the first and second follow-up are seen in Table 2. In comparison with adverse effects in both drug groups, a statistically significant difference was found only in erythema at first follow-up (Mann–Whitney, $P = 0.019$).

Discussion

There is inadequate information available at present to determine the best treatment for melasma. There are a wide range of treatments available, responses to which are variable.[20]

Azelaic acid is a depigmenting agent that acts as a tyrosinase inhibitor without resulting in a potentially dangerous side effect of exogenous ochronosis, as is reported with the use of topical hydroquinone.[21] It has also been reported to have an inhibitory effect on the DNA synthesis of melanoma cell lines,[22] but the entire mechanism of action for azelaic acid is not fully understood.[10] It has no depigmenting effect on constitutive skin color, showing that its activity is specific to hyperfunctioning and abnormally proliferating melanocytes.[11]

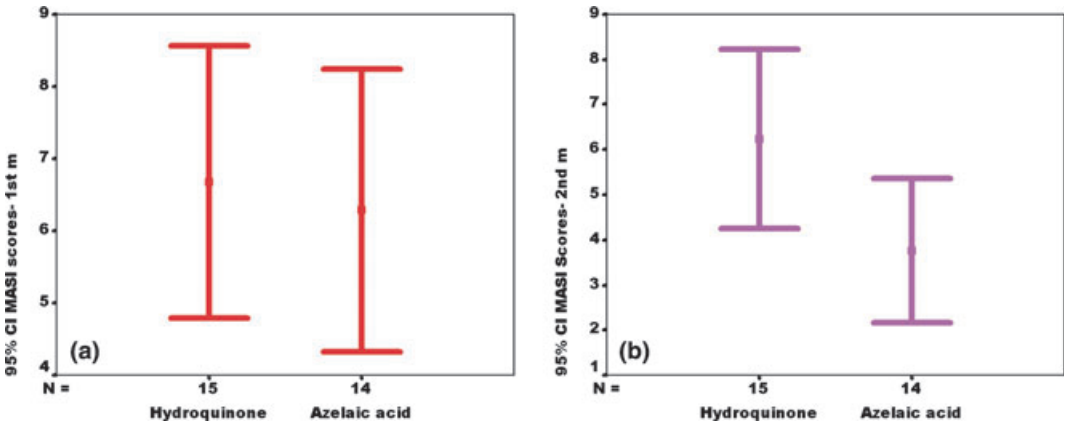

Figure 1 Comparative error bars of hydroquinone and azelaic acid effectiveness at first (a) and second (b) months of therapy.

Table 1 Hypopigmentation grading in hydroquinone (HQ) and azelaic acid (AZA) groups at first and second follow up period

	First follow up				Second follow up			
	HQ		AZA		HQ		AZA	
Hypopigmentation grading	No	%	No	%	No	%	No	%
1	4	26.7	2	14.3	2	13.3	0	0
2	8	53.3	8	57.1	10	66.7	6	42.9
3	3	20	4	28.6	3	20	8	57.1
4	0	0	0	0	0	0	0	0
Total	15	100	14	100	15	100	14	100

(1) no effect (no visible changes of pigmentation); (2) mild (decrease of visible pigmentation, but there is still some visible border); (3) moderate (marked decrease of visible pigmentation, but there is still some visible border); and (4) excellent (a complete loss of visible abnormal pigmentation).

It has been shown that azelaic acid is a scavenger of harmful free radicals, and it has an inhibitory action on neutrophil-generated reactive oxygen species, so these properties may make it useful for treating inflammatory conditions and a variety of other conditions involving excessive generation of free radicals.[16]

Azelaic acid was reported to have a better effect than hydroquinone 2% in a double blind study,[23] but a similar efficacy was observed between azelaic acid and hydroquinone 4% in Balina and Graupe's study in 1991.[24] In these studies, the azelaic acid 20%, hydroquinone 2%, and 4% creams were applied twice daily for 24 weeks.

In the other study, a combination of azelaic acid 20% and glycolic acid 15–20% was reported as equally effective as hydroquinone 4% cream in the treatment of hyperpigmentation in darker skinned patients after use for 24 weeks.[13]

In our study, no significant difference was found between MASI scores of these two drug groups at the first follow-up period, but at the second month, we found a significant difference between azelaic acid and hydroquinone group with respect to MASI scores. In this study, all patients had epidermal type of melasma and they also had mild melasma, which leads us to believe that this discrepancy between our study and the older ones is because of melasma type. In the aforementioned studies, the method of evaluation is a five-point scale measured according to physicians' subjective evaluations; they did not calculate MASI scores, and it seems as if this may be the other possible reason for the difference between the present study and the older ones.

However, the same sunscreen was used in both treatment groups, and the difference in the overall results reflects differences in the therapeutic activity of the two trial preparations. Azelaic acid 20% might induce better response than hydroquinone 4% in epidermal and mild types of melasma, and the nontoxic properties of azelaic acid may be advantageous in the prolonged frequently repeated treatment of melasma. It

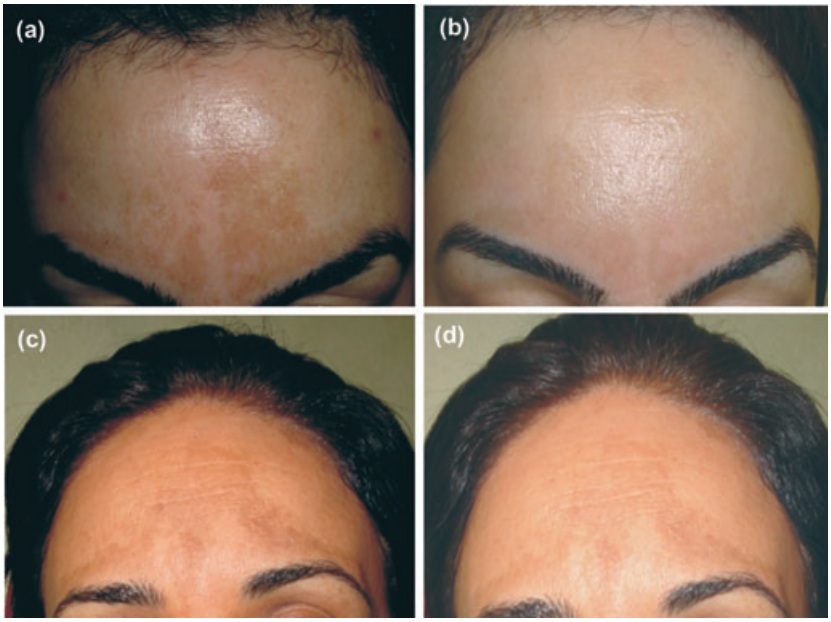

Figure 2 A patient in azelaic acid group (a, before treatment, b, after 2 months therapy) and a woman in hydroquinone group (c, before treatment, d, after 2 months therapy).

Table 2 Adverse events of azelaic acid (AZA) and hydroquinone (HQ) at first and second follow-up period

	First month				Second month			
	AZA		HQ		AZA		HQ	
	No	%	No	%	No	%	No	%
Erythema	1*	7.3	7*	46.6	0	0	2*	13.3
Irritation	5*	35.7	9†	59.9	2*	14.3	7*	46.6
Pruritus	1*	7.3	3*	20	0	0	1*	6.6

*Grade 1.
†Represents one patient grade 2 and 8 of them grade 1.

should thus be prescribed for patients for whom several months of continuous treatment may be required to achieve the desired results. In our study, complete clearance of melasma was not shown in any patient in either group, which may be a result of the short duration of the treatment.

The colorimeter was not used in this study, which represents the most important limitation of this study. Only epidermal types of melasma were included, and this might be the other limitation.

In Balina and Graupe's study,[24] local irritation was reported more frequently with azelaic acid, and allergic sensitization was observed only with hydroquinone. Overall side effects in this trial are mild and transient, but the adverse effects of hydroquinone were reported to be more severe than those of azelaic acid.

In conclusion, this study suggested that 20% azelaic acid cream applied twice daily over a period of 2 months and used concomitantly with a broad-spectrum sunscreen is effective in reducing mild melasma. Lightening of melasma was better in the azelaic acid group than in the hydroquinone group, but a continuous treatment for several months may be required to achieve the desired results. In addition, for a more conclusive result, large blinded controlled trials are needed.

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