

Therapeutic efficacy of a cream based azelaic acid 20% versus hydroquinone 4% in patients with melasma

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Background: Melasma is an acquired therapeutically problematic disease characterized by symmetrical facial hypermelanosis. The aim of this study was to evaluate the efficacy of azelaic acid 20% cream in the treatment of melasma in Iranian patients and compare it with hydroquinone 4% cream which has been the standard treatment.

Method: The study was an open clinical trial with a split-face design. All patients applied hydroquinone 4% cream on the right side and azelaic acid 20% cream on the left side for 20 weeks. Modified melasma area and severity index (mMASI) was determined for each patient at the beginning and at the end of study and compared statistically.

Result: Thirty-three patients were included in the study. Although both medications were effective in reducing mMASI, there was no statistical difference between the two (P value=0.6). Overall, 69.7% of the patients on the hydroquinone 4% side and 63.6% on the azelaic acid 20% side showed good to excellent response. The subjective patient assessment of improvement was 75.7% for hydroquinone 4% and 66.6% for azelaic acid 20%.

Conclusion: Both topical hydroquinone 4% and topical azelaic acid 20% had almost similar effects. Considering the relatively less known side effects of azelaic acid compared to hydroquinone, it can be an appropriate substitute in the treatment of melasma.

Keywords: azelaic acid, hydroquinone, melasma, treatment

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INTRODUCTION

Melasma is a common acquired hypermelanosis that occurs exclusively in sun-exposed areas. It is exacerbated by sun exposure, pregnancy, contraceptive pills and certain anti-epileptic drugs. Melasma is more common among darker skin types (skin types IV to VI) as in Asians, especially Middle Eastern population. It is one of the major causes of dermatologic visit in women and high cost value therapies for patients although men also may suffer from the condition ^{1,2}.

Successful treatment of melasma involves the triad of sunblocks, bleach and time. Bleaching

preparations include 2 or 4% hydroquinone (HQ)-containing creams. The higher concentrations carry more risk of contact dermatitis, rebound upon discontinuation, exogenous ochronosis and occasional hypopigmentation ³. Topical azelaic acid (AZA), which inhibits DNA synthesis and mitochondrial enzymes and therefore induces the direct cytotoxic effects toward the melanocyte, also has a modest antityrosinase activity. It may have a lower risk of lightening the normal skin than HQ as it has no depigmenting effect on the normally pigmented skin; this specificity may be attributed to its selective effects on abnormal melanocytes ². This study was performed to evaluate and emphasize

the effect of topical AZA in Iranian patients with melasma. Several clinical studies ^{4,5} have shown its efficacy but it is not yet approved by the US Food and Drug Administration (FDA) for the treatment of melasma ⁶.

PATIENTS AND METHODS

This study was an open clinical trial with the comparison of the left and right side of the face. The protocol was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences. All patients with bilateral epidermal and/or mixed melasma referring to Shahid Faghihi and Shahid Mottahari dermatology clinics affiliated to Shiraz University of Medical Sciences were considered. The pregnant and lactating women and those on oral contraceptive pills were excluded. After receiving information about the study, the remaining 44 patients (42 women and 2 men) signed informed consent forms. The patients were instructed to apply HQ 4% cream to the right and cream based AZA 20% to the left side of the face each night for 20 weeks. All participants used a suitable sunscreen cream with SPF 30 and were asked to reapply it every 3 hours.

Before entering the study, age, sex and duration of melasma were recorded and wood's lamp examination was done. Melasma lesions are scored by MASI formulated by Kimborough- Green as the following ⁷:

$$0.3 (D_F + H_F) A_F + 0.3 (D_{MR} + H_{MR}) A_{MR} + 0.3 (D_{ML} + H_{ML}) A_{ML} + 0.1 (D_C + H_C) A_C$$

F= Forehead, MR= Right Malar, ML= Left Malar, C= Chin

D= Darkness (0-4), H= Homogeneity (0-4), A= Area ¹⁻⁶

As mentioned earlier, the study was done by comparing the right and the left side so MASI was modified to mMASI as follows:

mMASI for the right side:

$$0.15 (D_F + H_F) A_F + 0.3 (D_{MR} + H_{MR}) A_{MR} + 0.05 (D_C + H_C) A_C$$

mMASI for the left side:

$$0.15 (D_F + H_F) A_F + 0.3 (D_{ML} + H_{ML}) A_{ML} + 0.05 (D_C + H_C) A_C$$

The patients were classified objectively in five groups on the basis of reduction in mMASI as follows:

Poor: 0-24% reduction in mMASI.

Fair = 25-49% reduction in mMASI

Good = 50-74% reduction in mMASI

Very good > 75% reduction in mMASI (but not complete recovery)

Excellent = Complete recovery

Also, a patient subjective assessment for treatment efficacy was done at the end as mild, moderate, good, and excellent response. Each patient was revisited at weeks 6, 10, 14, and 20. Melasma was scored at weeks 0 and 20, but side effects as redness, itching, burning, scaling, and development of any papule or vesicle were noted at each visit. Statistical analysis was done by parametric paired t-test.

RESULTS

Only 33 patients (all women) completed the study. Two in the HQ region (group), 3 in the AZA region (group), and one in whole face (both groups) developed side-effects necessitating discontinuation. Two patients dropped out due to mistake in the usage of creams and three due to unknown reasons. The age range was 19-45 years with a mean of 32.7±6.4 years and the duration of melasma was 1-16 months with a mean of 6±1.9 months.

The treatment results are summarized in tables 1 and 2. As it is shown, the mean reduction of mMASI in the AZA group and HQ group were 4.41 (55%) and 4.69 (61%) respectively with no statistically significant difference (P. value=0.61). Objective

Table 1. mMASI score before and after treatment, and its reduction in each treatment group.

Treatment group	mMASI score			
	Before treatment mean (range)	After treatment mean (range)	Reduction	Percentage of reduction (%)
Azelaic acid 20%	7.88±3.27 (2.75-16.2)	3.47±2.88 (0-11)	4.41	55%
Hydroquinone 4%	7.8±3.36 (3-17)	3.11±2.91 (0-11)	4.69	61%

Table 2. Clinical efficacy and objective response in each treatment group according to reduction in mMASI.

Treatment group	Objective Response					Total
	Excellent	Very good	Good	Fair	Poor	
AZA No (%)	4 (12.1)	7 (21.2)	10 (30.3)	9 (27.3)	3 (9.1)	33 (100%)
HQ No (%)	6 (18.2)	9 (27.3)	8 (24.2)	7 (21.2)	3 (9.1)	33 (100%)

response to treatment as studied by decrease in mMASI scoring after 20 weeks is shown in Table 2.

In evaluating the patient subjective assessment of treatment efficacy, 25/33 (75.7%) in HQ group vs 22/33 (66.6%) in AZA group reported good or excellent response.

As previously mentioned, 6 patients (2 in the HQ group, 3 in the AZA group, and 1 in both groups) showed some degrees of adverse effects as erythema, burning, and itching necessitating discontinuation. Also, 3 other cases in each treatment group showed mild erythema which disappeared upon continuation. No papulo-vesicular lesions or desquamation were noted.

DISCUSSION

Melasma is a common acquired symmetrical hypermelanosis characterized by irregular light to dark brown macules and patches on sun-exposed areas of the skin. On histopathology, there is epidermal hyperpigmentation, an increased number of melanocytes and an increased activity of melanogenesis overlying dermal changes caused by solar radiation⁸.

HQ has been used since 1950 in commercially available over-the-counter skin lightener products and since 1960 as an available medical product. Beginning in 2001, HQ is no longer authorized for use in cosmetic skin lightening formulations in European Union countries⁹ which is because of the effects such as leukoderma-en-confetti, occupational vitiligo and exogenous ochronosis. However, recent literature search suggests that possible long-term effects such as carcinogenesis may be expected, as well. Metabolites of HQ formed in the liver are mostly responsible for carcinogenesis. Although there is no report yet demonstrating carcinogenesis resulting from its application on the skin, we should be aware of this potential risk¹⁰.

AZA, a saturated dicarboxylic acid, is shown to be a competitive inhibitor of tyrosinase and membrane-associated thioredoxin reductase, which

is essential for electron donor for the ribonucleotide reductase and regulation of DNA synthesis¹¹. It is used in the treatment of patients with acne vulgaris and it was concluded that AZA 20% topical cream was as effective as clindamycin 1% lotion for treating acne lesions in a clinical trial performed on 108 patients with mild and moderate acne¹².

Clinical studies of patients with melasma have shown that topical AZA 20% is superior to HQ 2% and as effective as HQ 4%, without the undesirable effects of HQ in different populations^{4,5}. In a clinical trial performed recently by Tehrani et al, it was shown that AZA 20% plus HQ 5% was more effective with a more rapid onset of therapeutic response as compared to HQ 5% alone (50% versus 35%) in the treatment of melasma¹³. On the other hand, AZA with tretinoin is more beneficial than AZA alone after 3 months¹⁴. In a prospective single-blind study, of the participants who received clobetazole propionate 0.05% cream for 8 weeks followed by AZA 20% cream for 16 weeks, 96.7% showed good to excellent response as compared to 90% of the patients who received AZA 20% for 24 weeks. The authors suggested that as response to AZA was rather slow, this sequential therapy added to the compliance of the patients¹⁵.

Our study showed the almost similar efficacy of HQ 4% and AZA 20% in the treatment of melasma in Iranian patients. We do not recommend adding topical steroid as a combination due to its frequent side effects as telangiectasia, atrophy and hypertrichosis, and also tretinoin because of its frequent irritation added to that of AZA. This study also showed the efficacy of AZA alone in the treatment of melasma; therefore, it is beneficial in patients with HQ sensitivity or those with contraindication to HQ as pregnant women.

As topical AZA is approved by FDA for the treatment of acne vulgaris and inflammatory (papulopustular) rosacea and considering the frequent side effects of HQ, we recommend AZA 20% as a safer substitute for HQ in the treatment of melasma and its possible approval.

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