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RESEARCH ARTICLE

T. S. Andrés *et al*, The *Experiment, 2014, Vol.25 (2)1711-1716*

EFFICACY AND TOLERABILITY OF AMINOACID FILAGGRIN BASED ANTIOXIDANTS COMPARED WITH HYDROQUINONE 4% CREAM IN SKIN TYPE IV (FITZPATRICK) MEXICAN WOMEN WITH MIXED, CENTROFACIAL MELASMA.

ABSTRACT

Background
Melasma is a common disorder of pigmentation, characterized by symmetric brown or brown-gray patches in sun-exposed facial areas. Hydroquinone (HQ) is the most effective agent in melasma treatment; however it has some adverse events (AE) that limit its extensive use. We evaluated the clinical response of aminoacid filaggrin-based antioxidants (AFBA) in Mexican patients with centrofacial melasma.

Methods
Fifty-three Mexican female patients with centrofacial melasma were included in this five-week, single-center, comparative, open-label study. The patients were divided into two groups. One group (twenty-eight patients) received AFBA once a week for five weeks and the second group (twenty-five patients) received HQ 4% cream once daily at night for five weeks.

Results
The AFBA group exhibited a baseline MASI score of 8.96 ± 4.83 and a 5-week MASI score of 4.99 ± 3.27. The HQ baseline MASI score was 7.32 ± 5.81 and a 5-week MASI score was 4.98 ± 4.2. No statistically significant differences were observed between the two groups according to the Melasma Area and Severity Index (MASI). There were more AE in the AFBA group compared with the HQ group (P= .001). The reported AE did not require further treatment or discontinuation in either group.

Conclusions
AFBA was as effective as HQ 4% cream, however AE such as itching and skin irritation were more frequently seen in the AFBA group, but such AE did not require treatment or withdrawal. Further controlled, blinded, multicenter studies are required to support these results.

key words. Melasma. Aminoacid fillagrin based antioxidants. Hydroquinone. Treatment

INTRODUCTION

Melasma is an acquired cutaneous hyperpigmentation with a negative impact on quality of life and should not be considered as a cosmetic problem. It is characterized by symmetric brown or brown-gray patches on sun-exposed skin (face, neck and arms). This condition is commonly seen in women (90% of cases) and in Fitzpatrick III-IV skin types. For this reason, it is commonly seen in Latin American women. [1-3]

The main objective of the treatment of melasma is to reduce the affected area and to clear the spots by decreasing melanocyte and melanosome proliferation, and promoting the degradation of the pigment. The main therapeutic options are the control of any causative factor (make-up, frictional, etc), the use of an adequate sunscreen according to skin type, and a variety of depigmenting agents. [4,5]

HQ is the most effective agent in the treatment of melasma, with AE such as skin irritation, burning, and itching. It has been used in double and triple combinations, with excellent results in different studies. [6-9]

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AFBA are carboxylated aminoacid with similarities to hydroxiacid, which promotes exfoliation and reduces cutaneous pigmentation. These chemical agents have been used in melasma treatment with an adequate safety and efficacy profile; however, there are few comparative studies, [10,11] and none in Mexican women.

This study evaluated the efficacy and tolerability of AFBA compared with 4% HQ in Mexican women with skin type IV, with mild to moderate facial melasma.

MATERIAL AND METHODS

Sixty-two Mexican female patients suffering from melasma were included in this open-label, randomized, comparative, single-center, five-week study. Inclusion criteria comprised female patients with mild to moderate bilateral, mixed melasma (determined by Wood´s lamp examination), aged 25-60 years, with skin type IV and a minimal surface area of $\geq 5cm^2$. Exclusion criteria included pregnancy, use of another topical agent within three months of the study, and other skin diseases in the site of treatment. All patients provided written informed consent prior to the enrollment. The study was approved by the Investigation and Ethics Committee at our hospital.

Methods

During the study, we performed standard photographs and the Melasma Area and Severity Index (MASI) score to accurately quantify the severity of melasma, according to the procedure modified by Kimbrough-Green *et al.* [12] Clinical assessments were recorded at baseline and every week during follow up (week 1, 2, 3, 4 and 5). Chromametry and other studies were not assessed.

The AFBA were applied as follows: in five weekly sessions, the peeling agent was applied to the entire face. The exposure time depended on the development of erythema and burning symptoms. The concentration of the amino-acids used was gradually increased according to patient tolerability and improvement during follow up. At the end of each session, the face of each patient was washed with tap water and sunscreen cream was applied gently.

The other group received 4% HQ cream which was applied by the patient at night. The type of treatment used by each patient was determined by a computer-generated randomization code. Only gentle cleansing was required before application; no further degreasing was performed.

Clinical assessment

Efficacy was evaluated by measuring MASI score at baseline and at weeks 1, 2, 3, 4 and 5. Response was graded as excellent (≥75-100% reduction of MASI score), good (≥50-74% reduction), fair (≥25-49%), or poor (<25%). Tolerability was assessed by determining local adverse events (dryness, erythema, swelling, hyper or hypopigmentation) on a 4-point scale (0= none to 3= severe). Overall safety was monitored through individual reporting of adverse events.

Statistical analysis

For comparative analysis between the different measurements, a Chi-square (categorical variables) and a Mann Whitney tests (numerical variables) were performed, using the statistical package SPSS (Version 17 for Windows, Chicago, Ill). All tests were two-sided, and the statistical difference was declared at a 5% two-sided level.

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RESULTS AND DISCUSSION

Results of the randomization process are shown in Figure 1. Sixty-two Mexican women were included, 55 with mild melasma (88.7%) and 7 (21.8%) with moderate melasma, according to MASI score. Baseline characteristics of the sample are shown in Table 1.

Fifty-three patients completed the study; 28 patients in the AFBA group and 25 in the HQ group (4 patients of the first group and 5 patients of the last group were lost on follow-up, the reasons were personal ones, not related to the study product).

Patients were assessed at baseline, with an average MASI score of 8.96 ± 4.83 (3.4-24) in the AFBA group and an average MASI score of 7.32 ± 5.81 (1.8-23.6) in the HQ group (*P*= .232); and weekly until 5 weeks of treatment, with an average MASI score of 4.99 ± 3.27 (0.6-10.1) in the AFBA group and an average MASI score of 4.98 ± 4.2 (0.9-19.6) in the HQ group (*P*= .991). When comparing MASI scores at 0 and 5 weeks in each group, we found that there were statistically significant differences in the clinical improvement of melasma on both groups (*P*= 0.001). {Fig 2}

Improvement was excellent in 1 patient (3%) using AFBA; none of the patients using HQ developed an excellent response; good response was observed in 12 patients (43%) using AFBA and 5 patients (20%) using HQ (*P*= .002); and fair in 10 patients (36%) using AFBA and 8 patients (32%) using HQ (*P*= .886). In 5 patients with AFBA (18%) the response was poor, compared with 12 patients (48%) using HQ (*P*= .001).

The incidence and description of adverse events to AFBA and HQ are shown in Table 2. The frequency of AE was higher in the AFBA group than in the HQ group. Erythema and scale were the most commonly reported AE. Burning symptoms were reported only in the AFBA group. The reported AE did not require further treatment or discontinuation in either group.

AFBA are carboxylated aminoacids with similarities to □-hydroxiacid, which promotes exfoliation, reduces the risk of residual pigmentation and are based in filaggrin, which is an epidermic structural protein, essential for the skin and part of the natural moisturizing factor. They have been used in 20-60% concentrations for cutaneous disorders like acne, rosacea and photoaging, mainly in patients with sensitive skin due to the presence of fewer AE. [10,11]

There are a few studies in the literature comparing AFBA with standard melasma treatments, [8,10] but none comparing AFBA with the gold standard, which is HQ.

Sanad *et al*,[10] compared AFBA with tricloroacetic acid (TCA) in 15-35% concentrations and glycolic acid (GA) in 20-70% concentrations. They found significant differences in the efficacy and onset of the improvement between treatments, with better results in AFBA than those with GA and TCA. Recurrence was recorded within 3-6 months in 4 patients (40%) treated with GA, 8 patients (80%) treated with TCA, while no recurrence was recorded in those treated with AFBA (this may be due to its antioxidant and moisturizing effects which protect patients from photosensitization). [10,11] AFBA are very effective in melasma, because they reduce photo-pigmentation with less irritation, often associated with other peeling agents, and with the same effect on all skin types. [11]

CONCLUSION

With the use of AFBA, AE such as itching and skin irritation could limit its extensive use, however, it offers a rapid depigmenting rate, and also, the weekly application was well tolerated in skin type IV and could promote adherence.

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TABLES

Variable	AFBA (n= 28)	HQ 4% (n= 25)	*P* value
Age, y	42.88 ± 6.84	44.83 ± 7.91	NS
MASI score ± SD	8.96 ± 4.83	7.32 ± 5.81	NS
Severity of melasma			
Mild (%)	24 (86)	21 (84)	NS
Moderate (%)	4 (14)	4 (16)	NS

y = years. SD = Standard deviation. AFBA = aminoacid filaggrin-based antioxidants. HQ = Hydroquinone. NS = Not significant.

Table 1. Data summary.

Adverse event	AFBA (n= 28)	HQ 4% (n=25)	*P* value
Skin irritation (dermatitis)	8 (32%)	4 (33%)	NS
Scaling	7 (28%)	4 (33%)	NS
Dry skin	3 (12%)	1 (8%)	NS
Pruritus	3 (12%)	3 (25%)	.001
Burning	4 (16%)	0	.001
Total adverse events	25	12	.001
Patients reporting adverse events	12 (43%)	7 (28%)	.001

NS = Not significant.

Table 2. Overview of safety of AFBA and HQ.

FIGURES

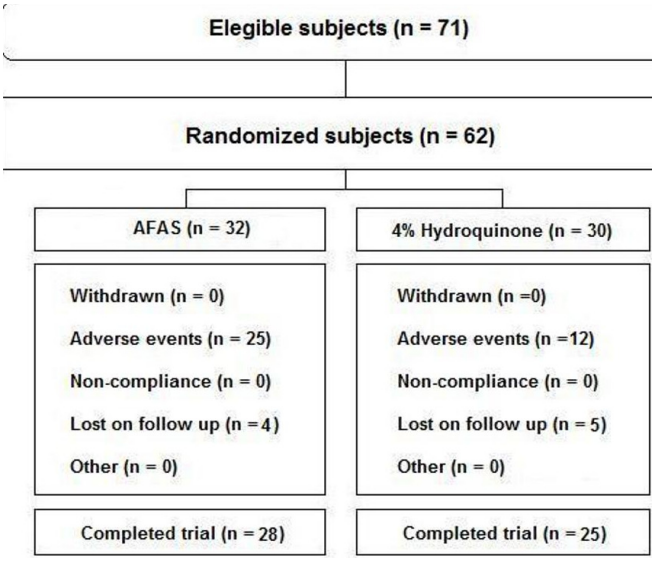

Figure 1. Flow chart of patients participating in the study.

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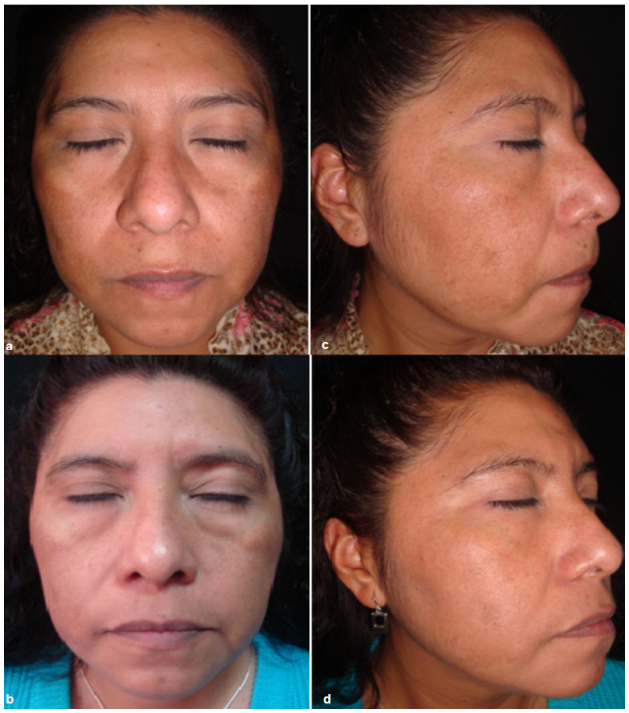

Figure 2. Photographs taken before (a, c) and after (b, d) treatment with AFBA.

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