Curierul medical, February 2016, Vol. 59, No 1

Comparative clinical study of depigmentation products on facial melasma in Latin women

***Cecilia ORLANDI-JORQUERA[1], María Gabriela MORAN-CARDENAS[2], Valery Magdalena ESCOBAR-HUENCHUL[3]**

[1]Orlandi Clinic, Santiago de Chile, Chile, [2]Dermatology Department, Pino Hospital, University of Santiago, Santiago de Chile
[3]Internal Medicine VII year, University of Diego Portales, Santiago de Chile, Chile
*Corresponding author: cecilia.orlandi@gmail.com. Received June 21, 2016; accepted July 29, 2016

Abstract

Background: Hyperpigmented lesions need the most frequent dermatological consultations, the acquired ones being more effectively treated. Out of them, the most common is melasma, which is currently treated with hydroquinone. Our objective was to compare the efficacy of a treatment based on Diacetylboldine-DAB, Alpha arbutin and Licorice with hydroquinone 4%.
Material and methods: We carried out a pilot study on 30 Latin patients (skin type III and IV after Fitzpatrick's classification). The product under study was applied on one side of the face and hydroquinone on the other, during 60 days.
Results: The study product demonstrated effectiveness comparable to 4% hydroquinone in the 60 days of monitoring time. The hyperpigmentations are of a chronic type and so, considering the formula of the study product, it has the great advantage of permitting use for a prolonged period of time without the risk of undesirable side effects such as ochronosis. Tolerance for the product was excellent as well, both for daytime and night-time formulations, and neither irritation reactions nor allergic reactions were present during the period of use.
Conclusions: The combined use of active substances is similar and comparable to hydroquinone in a 60 day period. The foundation can be laid for future studies to approach a new investigation with a larger number of patients, in which the use of hydroquinone can be established in comparison with this new treatment, so as to allow a statistically significant relationship to be established. Additionally, by studying a larger number of participants, it would allow this new product to be set up as an effective alternative treatment for melasma.
Key words: facial melasma, antipigment skin agents.

Introduction

Hyperpigmented lesions, especially on the face, are a very common reason for consultation in dermatology. Some spots are of the congenital type and others are acquired; the latter type is relatively more susceptible to effective treatment. Among these we find melasma, ephelides or freckles, lentigines, postinflammatory hyperpigmentations and others [1].

Melasma or facial chloasma is a commonly acquired hyperpigmentation related to an increase in the number and activity of clones of melanocytes, when activated by ultraviolet light. It appears in exposed areas and can be classified, according to location, as centrofacial (the most common), malar or mandibular. It can also occur on the neck and forearms [1, 2, 3, 4].

This pathology is predominant in the female sex, appearing in 10 women for each man, thus highlighting the role played by oestrogen in stimulating melanogenesis, possibly by costimulation in the synthesis of melanosomes [5, 6].

Factors such as exposure to the sun, stress, pregnancy, oral contraceptives, anti-epileptic drugs, endocrine dysfunction, cosmetics, nutritional deficiencies and liver deficiencies have been associated with clinical aggravation of melasma [7].

In the physiopathology of the formation of melasmas in predisposed persons, the action of sunlight on a chemical substrate in areas exposed to light has been established, with presentation increasing during periods of exposure to ultraviolet rays, and decreasing when the patient avoids ultraviolet rays.

Acute exposure to ultraviolet radiation activates one of the most important adaptive mechanisms of the skin, the process of inflammation-tanning, as well as inducing pigmentation in the areas subjected to damage. The increased deposit of melanin can be epidermal, dermal or a mixture of the two [1, 8].

Diagnosis is essentially clinical and it is indispensable that the examination takes place under good lighting. Additionally, other instruments can be used such as a magnifying glass (magnified 7-10x) or a dermatoscope (epiluminescent microscope) using wide field objectives with a focal distance of 10 – 15 cm; magnifications of 10 to 50x are routinely enough to permit observation of dermoepidermal pigmentation lesions, along with a Wood's lamp which is a Hg lamp encased in glass that emits UV radiation with a peak of 360 nm, enough to penetrate into the medium dermis. It allows visualization of the level of pigmentation, differentiating epidermal hyperpigmentation, which increases the contrast in the lesion, from dermal hyperpigmentation, which has no contrast. There is a clinical correlation between this procedure and a histopathological biopsy. Instruments can also be used to evaluate the color of skin, by the presence of melanin, and that allows quantitative evaluation of the treatments used [1, 8, 10].

To treat melasma, suspension of oral contraceptives is recommended, whenever possible, although the pigmentation may last several years in spite of this. Direct exposure to the sun should be avoided, broad-spectrum sunscreen should be used and physical measures, such as wearing a hat, should be taken. Several products exist for topical use, the most common being 2 to 4% hydroquinone, considered the standard in the Western Hemisphere (prohibited in Japan). It can be associated with tretinoin, kojic acid, glycolic acid, arbutin,

ascorbic acid, licorice, ellagic acid, azelaic acid, pycnogenol, etc. [11, 13, 14].

Hydroquinone is approved by the FDA in humans in concentrations equal to or less than 2%, and in higher concentrations only under medical supervision. Other treatments can be added such as chemical and mechanical peelings and laser treatments [15, 16, 17].

General Objective of the Study: to confirm clinical efficacy and tolerance of a treatment based on a formulation with the following components: Diacetylboldine - DAB, Alpha Arbutin, and Licorice (see detailed formula in appendix), to reduce hyperpigmented lesions of the melanosis or facial melasma types, through non-invasive technologies, in Latin women.

Specific Objectives: to compare the efficacy of the product in the study to 4% hydroquinone in a compounded formulation. To evaluate the number of spots and intensity of pigmentation through non-invasive technologies and the cosmetic properties of treatments to be used (self-completed questionnaire).

Material and methods

An open prospective study was performed on 30 volunteers with hyperpigmented lesions that persisted despite receiving other treatments, to confirm the clinical efficacy of a treatment based on a depigmentation product applied at night, formulated with a base of Diacetylboldine - DAB, Alpha Arbutin, Licorice, Glycolic Acid, Ascorbic Acid and Salicylic Acid, plus a depigmentation product applied during the day, formulated with a base of Diacetylboldine - DAB, Beta white®, Vitamin C and 50+ sunscreen.

Patients applied products on one half of the face, to compare their effect with hydroquinone in a 4% compounded formulation on the other half of the face, for a period of 60 days. All patients received UV protection with 50+ broad-spectrum sunscreens (fig. 1). The parameters to be studied were evaluated through clinical examinations, instrumental methods and a self-evaluation questionnaire.

The study was performed over a period of 60 days with a total of 30 female patient volunteers of Latin background. Treatment with the formula took place with applications during the day and at night. The test product was applied according to the manufacturer's instructions and a self-evaluation questionnaire was used for subjective appreciation of the product, cosmetic acceptability of the formulation's appearance, texture and ease of application, presence of greasy residue, perception of odour and subjective evaluation of the efficacy of the product (reduction of spots). Additionally, adverse reactions during the study period (burning, itching and peeling) were evaluated and analyzed to determine any possible relation to product usage. Patients were selected in accordance with the following criteria:

Inclusion criteria – Female volunteer patients aged between 30 and 65 years, diagnosed with moderate to severe melasma, with or without lentigos or ephelides, who presented resistance to other treatments for melasma. They also must have complied with the criteria for being under contraceptive treatment or treatment for menopause, without a change in hormonal therapy, if any, during the 6 months before the study or during the study. They must not be pregnant or breast-feeding, not be using topical or systemic treatments at the start of the study, nor present a history of intolerance to topical products. Also, they were requested to abstain strictly from direct exposure to the sun and to sunlamps during the study period.

Exclusion criteria – patients undergoing treatment for their melasma. Subjects with a history of allergic reactions to depigmentation products were also excluded, as well as women who presented any systemic or cutaneous pathology or who received any medication that might have altered the evaluation parameters during the study period. Patients must not present active facial lesions, or any history of laser treatment, or chemical peeling in the two months prior to the study. Patients who may have used isotretinoin in the 6 months prior to the study, or who may have used steroids, alpha/beta hydroxy acids, or tretinoin in the two months prior to the study, were also excluded.

Patients signed an informed-consent form, notifying them of what to expect from the experience and of the possible consequences of their participation. It is used to give agreement to participate in the study. This consent agreement also informed them that participants' rights would be protected and that the data collected would remain confidential, although it may be used in an anonymous form in scientific studies. The decision to participate was entirely voluntary.

Prospective study that included 30 women volunteers of Latin descent, between 30 and 65 years of age, suffering from moderate to severe melasma on at least both of their cheeks. For the comparison study, a depigmentation product for night-time application was used, which was formulated on a base of diacetylboldine, alpha arbutin, licorice, glycolic acid, vitamin C and salicylic acid (see appendix for formula) along with a depigmentation product for daytime application, formulated on a base of diacetylboldine, Beta White® (a biomimetic peptide encapsulated in liposomes), vitamin C and sunscreen (see appendix for formula). These products were compared with a cream in a compounded formula associated with 4% hydroquinone. Face cleanser, humectant-based cream and 50+ invisible fluid sunscreen were used as part of the regular daily routine. This study was approved by the research ethics committee.

A Wood's lamp was used to determine the type of melasma, and a melanometer (Mexameter) from Khazaka-Courage was used to measure the quantity of melanin and to report the results obtained as a numerical value. The VISIA system was also used to evaluate pigmentation, along with other skin parameters. This system photographs the forehead and right and left sides of the face, which are evaluated by the system's software, which then issues numerical values that relate to average values in the general population of the same age and skin type. It also evaluates the effect of the applied treatments by comparing values issued by the system before and after application of the product in the study.

Digital photos were taken before and after treatment and a subjective evaluation was made by the participating patients

(self-evaluation). Skin phototypes were determined using the Fitzpatrick scale.

Types of skin:

I. Always burns, never tans
II. Always burns, tans slightly
III. Sometimes burns, always tans
IV. Never burns, always tans
V. Always deeply pigmented
VI. Black

Volunteers were evaluated on D 0 and D 60. At the initial visit patients were examined to clinically determine the type of melasma with a Wood's lamp, and parameters were measured by melanometer and with VISIA.

Pigmented lesions present on the right and left cheeks were evaluated clinically and classified as follows:

++++ If pigmented lesions were detected on 75% to 100% of the malar area.

+++ If lesions cover 50% to 75% of the malar area.

++ If lesions cover 25% to 75% of the malar area.

+ If lesions cover less than 25% of the malar area.

Digital photos were taken, and the products included in the protocol were delivered with instructions in their use.

Participants were instructed to report any discomfort that might be due to use of the study product, or if they had questions about their use.

At night, skin cleansing and application of the study product on the right side of the face and the compounded product on the left side, according to the attached diagram.

In the morning, skin cleansing and application of the study product on the right side of the face and base cream on the left side.

50+ fluid sunscreen on the whole face. Make-up as usual. In the examination after 60 days the same parameters were evaluated.

Results

At the beginning of the study the group of patients suffering from facial hyperpigmentation was composed of 30 healthy women, from 33 to 65 years of age, averaging 46,6 years of age, who met the inclusion criteria. 29 of them completed the study. One patient did not attend the examinations because of an illness unrelated to the study in progress.

The Wood's lamp test was applied to the patients, the result of which was compatible with pigmentation mostly of an epidermal character, making clear a major contrast with the pigmented areas when illuminated with this wavelength. Patient 17 did not attend the examinations.

As we see in table 1 of clinical measurement, of the 29 patients who completed the study, 11 patients improved on both sides of the face, 8 patients remained the same on both sides, 5 patients improved only on the right side, corresponding to the study product, 3 patients remained the same on the right side, corresponding to the study product, 2 patients worsened on the right side, corresponding to the study product, 3 patients improved only on the left side of the face, corresponding to hydroquinone, 7 patients remained the same only on the left side of the face, corresponding to hydroquinone. No patient worsened with the use of hydroquinone. An example of the clinical result can be seen in figure 2.

This measurement shows the pigmentation in the evaluated areas in numerical values, numbers that are correlated with clinical evaluation. The pigmented lesions do not disappear, but they do decrease in intensity. The effect can be seen in figure 3 (results with VISIA).

In this table we can see the measurement of melanin on the right and left halves of the face, in which measurements at 4 points on each cheek are averaged. A numerical figure is given that allows comparison of the intensity of melanin pigmentation on the cheek before and after treatment.

A comparative study was made through percentage variance analysis, with the numerical data issued by VISIA (tab. 2, 3). With this data we can emphasise the fact that a 19.7% improvement was made with respect to the initial value in the group of patients who showed improvement with the study product.

By the same analysis, in the patients that improved with hydroquinone, an 18.3% improvement was made with respect to the initial value.

In general, in the self evaluation, patients reported that the melasma affected their quality of life, a significant percentage going so far as to admit they use make-up to try to cover the damaged areas (fig. 4, 5).

Moderate itching and burning were described as adverse reactions to use of the study product, but not to the point of causing participants to decide to discontinue using the product (fig. 6, 7, 8). Furthermore, improvement was shown in areas such as skin texture, increased shine, and improved appearance, even though the hyperpigmented lesions did not necessarily disappear. This effect can also be seen in digital photos as in figure 2.

Even though minor adverse reactions existed that were well tolerated by patients, the majority of them stated that because of the improvement in skin quality from using the product for the established period of time, they would continue to use the product for a longer time. The cosmetic properties of the study product were very well evaluated by the patients.

FORMULAS OF STUDY PRODUCTS

Night time:

- Glycolic Acid 6%
- Lumiskin™ 4% (Diacetylboldine - DAB)
- Vitamin C (ascorbyl tetraisopalmitate) 2%
- Alpha Arbutin 2%
- Salicylic Acid 0.1%
- Licorice 0.1%

Day time:

- Beta white® 5% (Bio-mimetic peptide encapsulated in liposomes)
- Lumiskin™ 4% (Diacetylboldine - DAB)
- Vitamin C (ascorbyl tetraisopalmitate)1%
- Eusolex 15%
- Tinosorb M 9%
- Tinosorb S 1.5%
- Titanium Dioxide 2%

Conclusions

The study product demonstrated effectiveness comparable to 4% hydroquinone in the 60 days of monitoring time.

We know that the hyperpigmentations are of a chronic type and so, considering the formula of the study product, it has the great advantage of permitting use for a prolonged period of time without the risk of undesirable side effects such as ochronosis.

Tolerance for the product is excellent as well, both for daytime and night-time formulations, and neither irritation reactions nor allergic reactions were present during the period of use.

With our study, the foundation can be laid for future studies to approach a new investigation with a larger number of patients, in which the use of hydroquinone can be established in comparison with this new treatment, so as to allow a statistically significant relationship to be established. Additionally, by studying a larger number of participants, it would allow this new product to be set up as an effective alternative treatment for melasma.

References

1. Ortonne JP, Bose SK. Pigmentation: dyschromia. Textbook of Cosmetic Dermatology, terceraedición. Baran R, Maibach H. Taylor&Francis. Abingdon, 2005;393-404.
2. Grimes P. Melasma: etiologic and therapeutic considerations. *Arch Dermatol.* 1995;131:1453-1457.
3. Lage D, Costa A. Melasma. En: Tratado Internacional de Cosmecéuticos, Adilson Costa, Edit. Guanabana Koogan, Río de Janeiro, 2012;534-540.
4. Sánchez N, Pathak M, Mihm M. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. *J Am Acad Dermatol*. 1981;4:698-710.
5. Cestari T, Arellano I, Hexsel D, Ortonne JP. Latin American Pigmentary Disorders Academy "Melasma in Latin America: options for therapy and treatment algorithm". *JEADV*. 22(7):760-772.
6. Vasquez M, Maldonado H, Benjamin C, Sánchez JL. Melasma in men: a clinical and histologic study. *Int J Dermatol.* 1988;27:25.
7. Inoue K, Hosoi J, Ideta R, et al. Stress augmented ultraviolet - irradiation-induced pigmentation. *J Invest Dermatol*. 2003;121:165-71.
8. Gilchrest BA. Localization of melanin pigmentation in the skin with Wood's lamp. *Br J Dermatol*. 1977;96:245-248.
9. Clarys P, et al. Skin Color Measurements: Comparison Between Three Instrument. *Skin Res Technol*. 2000;6:230.
10. Grimes PE, Camarena E, Elkadi T. Colorimetric Assessment of Pigmentation and Erythema Using the Mexameter MX16 Correlation with Fitzpatrick's Skin Type and Race. Poster Exhibit, American Academy of Dermatology, 2000.
11. Haddad AL, Matos LF, Brunstein, et al. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone versus placebo in the treatment of melasma. *Int J Dermatol.* 2003;42(2):153-6.
12. Ni Z, Mu Y, Gulati O. Treatment of Melasma with Pycnogenol. *Phytother Res.* 2002;16:567-571.
13. Hurley ME, Guevara IL, Gonzales M, Pandya A. Efficacy of Glycolic Acid Peels in the Treatment of Melasma. *Arch Dermatol.* 2002;138:1578-1582.
14. Yoshimura K, Harii K, Masuda Y, et al. Clinical trial of bleaching treatment with 10% alltrans retinol gel. *Dermatol Surg.* 2003;29(2):155-6.
15. Cotellessa C, Peris K, Fargnoli MC, et al. Microabrasion versus Microabrasion Followed by 15% Trichloroacetic Acid for Treatment of Cutaneous Hyperpigmentation in Adult Females. *Dermatol Surg.* 2003;29:352-356.
16. Kawada A, Shiraishi H, Asai M, et al. Clinical Improvement of Solar Lentigines and Ephelides with an Intense Pulsed Light Source. *Dermatol Surg.* 2002;28:5.
17. Angsuwarangsee S, Polnikorn N. Combined Ultrapulse CO2 Laser and Q-switched Alexandrite Laser Compared with Q-switched Alexandrite Laser Alone for Refractory Melasma: A Split Face Design. *Dermatol Surg.* 2003;29:59-64.

Conflict of Interest

The authors declare that they do not have any conflicts of interest.

The article is offered for publication by pharmaceutical company "Becor"