Original Article

Avaliação da melhoria na qualidade de vida de portadoras de melasma após uso de combinação botânica à base de Bellis perennis, *Glycyrrhiza glabra e Phyllanthus emblica* comparado ao da hidroquinona, medido pelo MELASQoL

Evaluation of quality of life improvement in melasma patients, measured by the MELASQoL following the use of a botanical combination based on Bellis perennis, Glycyrrhiza glabra e Phyllanthus emblica.

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ABSTRACT

Introduction: Melasma is a common hypermelanosis that mainly affects women and has a negative impact on the quality of life. It is a chronic and recurrent condition, and a number of treatments have already been proposed.

Objective: Assessment of quality of life for women with melasma before and after treatment with botanical extracts and hydroquinone.

Methods: A clinical, phase IV, randomized, blinded study was conducted at a clinical research institute. Women (n = 56) aged 18-60, with phototypes I-IV, were randomized into two groups (epidermal or mixed melasma). The Melasma Quality of Life Scale was used to compare the patients' quality of life before and after the use of Bellis perennis, Glycyrrhiza glabra and Phyllanthus emblica botanical extracts twice a day (Group A), or 2% hydroquinone used at night (Group B). The Melasma Area and Severity Index was used to assess the treatments' efficacy.

Results: Appearance, frustration, embarrassment and feeling less attractive were the Melasma Quality of Life Scale variables that had the greatest negative impact on quality of life at the beginning of the study. After 60 days of treatment, there was improvement in all MELASQoL aspects, with no statistical differences between the two groups.

Conclusion: The improvement in melasma patients' self esteem provided by the use of the botanical extracts matched that of 2% hydroquinone.

Keywords: *melasma; quality of life; phyllanthus emblica.*

RESUMO

Introdução: *Melasma é hipermelanose comum que afeta principalmente mulheres e gera impacto negativo na qualidade de vida. É doença crônica, recorrente, e diversos tratamentos já foram propostos.*

Objetivo: *Avaliação da qualidade de vida de mulheres com melasma antes e após o tratamento,com extratos vegetais ou hidroquinona.*

Métodos: *Trata-se de estudo clínico, fase IV, comparativo, prospectivo, randomizado, monocego, monocêntrico, realizado em instituto de pesquisa clínica. Foram randomizadas em dois grupos 56 mulheres, com melasma epidérmico ou misto, entre 18 e 60 anos, fototipos I a IV. Utilizou-se o MELASQoL como instrumento para avaliar a qualidade de vida dos pacientes com melasma, antes e após o uso da associação dos extratos botânicos de Bellis perennis, Glycyrrhiza glabra e Phyllanthus emblica, aplicada duas vezes ao dia (grupo A), em comparação com o da hidroquinona 2% aplicada à noite (grupo B). O MASI foi o padrão de eficácia clínica utilizado.*

Resultados: *Das variáveis do MELASQoL, aparência, frustração, constrangimento e sentir-se menos atraente apresentaram maior impacto negativo na qualidade de vida no início do estudo. Após 60 dias de uso do produto houve melhora em todos os aspectos do MELASQoL, em ambos os grupos, sem diferenças estatísticas entre eles.*

Conclusão: *O uso da associação dos extratos botânicos de Bellis perennis, Glycyrrhiza glabra e Phyllanthus emblica melhora a autoestima dos pacientes com melasma tanto quanto o da hidroquinona 2%.*

Palavras-chave: *melasma; qualidade de vida; phyllanthus emblica.*

INTRODUCTION

Melasma is a common hypermelanosis characterized by hyperchromic brownish macules. It occurs mainly in the face but can also affect the arms; however, it is not found in the mucus membranes.[1-10] It can occur in three forms on the face: centrofacial (the most frequent pattern, affecting the malar, forehead, supralabial, nasal and chin regions); malar (the second most frequent pattern, affecting the zygomatic regions); and mandibular (affects the masseterian and infrabuccal regions).[2,3,10]

The term *melasma* derives from the Greek *melas*, which means "black."[2,3] It usually occurs in women of childbearing age that have intermediate phototypes (chestnut brown to red skins), of Hispanic or Asian origins, who live in tropical regions. It presents a higher frequency among those of Latin descent, and rarely occurs in men.[1-3,5,6,8,11] Melasma's prevalence is not yet precisely known.[2]

Although its etiopathogeny is not fully understood, [1,2,4] many of the disorder's contributing factors have been identified: solar radiation, genetic predisposition, pregnancy, estrogen and progestogen, endocrinologic disorders, cosmetics and phototoxic drugs.[1-5,8-14] Using Wood light, it is possible to classify melasma as epidermal, dermal, mixed or indeterminate.[3] Epidermal melasma is the most common type, and responds better to treatment. Wood's light intensifies the pigmentation, which is located in the epidermis. The dermal type of melasma is not intensified when illuminated with Wood's light, while in the mixed type, some areas are intensified and others are not. That examination becomes less effective in intensely dark skin types, and results in the melasma being classified as indetermined.[3,10] Dermal melasma is more resistant to treatment, due to its dependence on the elimination of melanin by the macrophages.[3] Melasma can also be classified as transient or persistent. When the hormonal stimulus is interrupted for one year and the melasma disappears, it can be classified as transient. Otherwise it is classified as persistent; solar radiation is one frequent causal factor.[3]

Melasma is a chronic and recurring disorder,[2,6-8,15] and there are several topical depigmenting agents that can be used in its treatment.[16] In addition, there are therapeutic options, such as microdermabrasion, chemical peels, intense pulsed light and lasers.1 The use of photoprotection against the sun is essential in its treatment.[2,17] Sunscreens containing physical blockers such as titanium dioxide and zinc oxide offer greater protection, and are therefore preferable to chemical protectors.[12] Hydroquinone, the most frequently used depigmenting drug,[5,9,17] inhibits tyrosinase and reduces the conversion of dopa to melanin. In addition, hydroquinone might inhibit DNA and RNA synthesis and destruct melanocytes and melanosomes.[3,18] The combination of hydroquinone with tretinoin and corticosteroid – as in the Kligman formula – increases its efficacy. [5,8] Side effects include irritation, erythema, colloid milium, ochronosis, post-inflammatory hyperpigmentation, irritant and allergic contact dermatitis, nail dyschromia, and confetti-type depigmentation, among others.[3,5,17] Such undesirable effects, in addition to the need for effective treatments, stimulate a great demand for new whitening products.

Emblica, liquorice and belides botanical extracts have whitening properties. Emblica has antioxidant effects and increases collagen production.[19] Liquorice inhibits tyrosinase (an enzyme that is integral in the formation of melanin) and has anti-inflammatory properties.[3,20] Belides play a role in the process of melanin formation.[18] If combined, these extracts can be an alternative treatment for melasma.[18]

Since melasma occurs mainly in the face and is very visible, it is an inconvenience for the patient. As a result, it negatively affects their quality of life and psychological and emotional well-being, and frequently leads the patient to seek the help of a dermatologist.[2,5,8,21,22] Facial lesions generate dissatisfaction, low self esteem, deprivation of social interactions and lower professional or academic productivity.[2,7]

This situation encouraged the development of a standardized and validated questionnaire to evaluate patients' quality of life. The Melasma Quality of Life Scale (MELASQoL) is a instrument that meets that need, comprising the three domains that are most intensely affected by melasma: social life, recreation/leisure and emotional well-being. [1,2,7,22,23]

The use of that questionnaire in countries where English is not the official language requires appropriate translation and cultural adjustments. It was translated into Brazilian Portuguese in 2006 (MELASQoL-BP), in compliance with the World Health Organization's rules.[6-8]

This study evaluated the quality of life of women with melasma before and after treatment with products containing vegetable extracts or hydroquinone.

METHODS

This was a phase IV, comparative, prospective, randomized, single-blind (only the investigator did not know the name of the product being analyzed), monocentric clinical study. It was approved by the Ethics Committee for Research in Human Beings.

Women (n = 56) aged 18-60, with phototypes I to IV, with epidermal or mixed melasma were selected. All participants signed a term of free and informed consent and agreed to take part in the study and to have their photographs published for scientific ends. All underwent a 60-day washout period with the isolated use of SPF 35 sunscreen, reapplied every two hours. The exclusion criteria were: pregnancy or breastfeeding; presence of active dermatoses in the area to be treated; previous adverse reaction to the formulas' agents; use of products containing vitamin C, azelaic acid, kojic acid, phytic acid, glycolic acid, anti-inflammatory and retinoid derivatives in the 30-day period preceding the washout.

The study participants were randomized to receive either a cream consisting of emblica depigmenting complex, liquorice and belides 7% (Clariderm Clear®, Laboratórios Stiefel Ltda., Guarulhos, SP, Brazil) twice a day (Group A) or 2% hydroquinone cream (Clariderm® cream, Laboratórios Stiefel Ltda., Guarulhos, SP, Brazil) during the night (Group B). The ins-

tructions received by the participants were the same as the recommended by the manufacturer for both products.. Both groups used the product for 60 consecutive days, together with sunscreen (SpectraBAN T® SPF 35, Laboratórios Stiefel Ltda., Guarulhos, SP, Brazil).

Five (twice monthly) follow-up visits took place during the course of the study; the product was distributed to the volunteer at the first visit. A physician conducted the clinical evaluations at the follow-up visits and assessed each patient's melasma as: worsened, stable, improved or improved considerably. In addition, photographs of the face were taken in the frontal, right and left positions at the beginning, halfway through and at the end of treatment, using a digital imaging device (Visia®, Canfield Imaging System, Fairfield, USA).

The MELASQoL was administered at each visit to evaluate patients' quality of life. The questionnaire has 10 questions on diverse aspects (skin appearance, frustration, embarrassment, depression, relationship with other people, desire to be with other people, feeling attractive, feeling less important and changes in one's sense of freedom), as demonstrated in Table 1. The final MELASQoL score can range between 7 and 70; higher values indicate worse quality of life.

RESULTS

Of the 56 volunteers, 50 (Group A: 23; Group B: 26) completed the study. Six were excluded for personal reasons. A 0.05% significance level and a 95% confidence interval were established. Since the Anderson-Darling test showed that the studied variables did not have a standard normal distribution, the non-parametric Friedman and Wilcoxon tests, in addition to the McNemar test of equality of paired proportions, were used.

In general, most MELASQoL questionnaire aspects presented significant improvement after 15 days of treatment, for both groups. Group A showed significant improvement in frustration (26.5% in 30 days of product use, p-value = 0.014), and significant improvement in the sensation of freedom (46.6% in 45 days, p-value = 0.006). Group B presented significant improvement in demonstration of affection (42% in 30 days of use, p-value = 0.002), improvement in feeling less important (34.6% in 30 days, p-value = 0.011), and improvement in the sensation of freedom (41.7% in 45 days, p-value = 0.016) (Figures 1 and 2). At the end of the study there was an average improvement of 63.64% in Group A, and 60.77% in Group B, including all parameters evaluated by MELASQoL, with no statistically significant between-group differences.

Chart 1: Quality of life questionnaire for melasma patients (MELASQoL)

Regarding your melasma condition, how have you been feeling during the last week, before this consultation?	**Not annoyed at all**	**Not annoyed most of the time**	**Not annoyed sometimes**	**Indifferent**	**Annoyed sometimes**	**Annoyed most of the time**	**Annoyed all of the time**
1. Your skin's appearance	1	2	3	4	5	6	7
2. Frustration due to your skin's condition	1	2	3	4	5	6	7
3. Embarrassment due to your skin's condition	1	2	3	4	5	6	7
4. Feeling depressed due to your skin's condition	1	2	3	4	5	6	7
5. Effects on relationships with other people due to your skin's condition (e.g., interaction with family, friends, personal relationships, etc)	1	2	3	4	5	6	7
6. Effects on your desire to be with other people due to your skin's condition	1	2	3	4	5	6	7
7. Your skin's condition hampers your expression of affection	1	2	3	4	5	6	7
8. The macules on your skin make you feel unattractive to others	1	2	3	4	5	6	7
9. The macules on your skin make you feel less important or productive	1	2	3	4	5	6	7
10. The macules on your skin affect your sensation of freedom	1	2	3	4	5	6	7

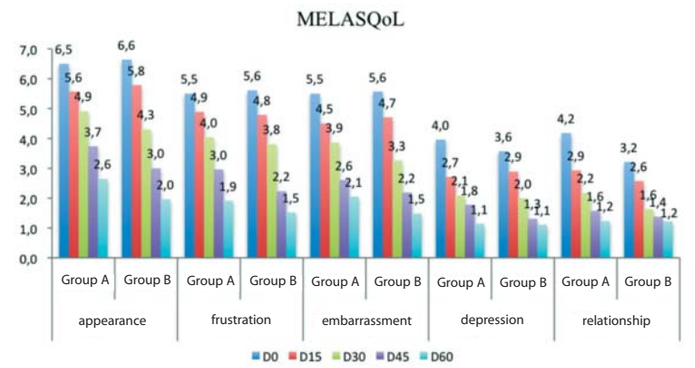

Figure 1: Appearance, frustration, embarrassment, depression and relationship items as evaluated by MELASQoL-BP

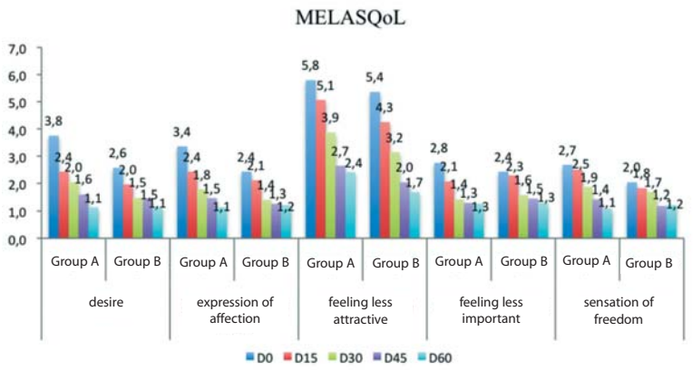

Figure 2: Desire, expression of affection, feeling less attractive, feeling less important and sensation of freedom items as evaluated by MELASQoL-BP

DISCUSSION

Melasma has been continuously studied, given that many factors are present in its etiopathogeny. Solar radiation is one of the most important factors contributing to its development and exacerbation.[3]

After repeated exposure to ultraviolet radiation, an increase in the number of melanosomes and active melanocytes takes place.[2] Melanosomes are organelles present within melanocytes, where the synthesis and storage of melanin occurs.[2] Tyrosine is the amino acid on which the enzyme tyrosinase acts, resulting in the formation of melanin.[2] Melanocytes have dendritic prolongations through which melanosomes are injected into the keratinocytes, and are distributed in the cytoplasm above the cell's nucleus.[2]

Melasma occurs more frequently among individuals with a family history of the condition, and among people of Hispanic and Asian descent .[2,3] In turn, the estrogen's action mechanism is likely due to the presence of estrogen receptors in melanocytes, which stimulate melanin production.[3] The expression of α-MHS (melanocortin) and MC1-R (melanocortin receptor) in melanocytes involved in the melasma's physiopathogeny[2] is increased by the hormone β-estradiol.[2]

Melasma is a common dermatosis. Studies show that affected patients feel annoyed and less attractive, and use cosmetics to cover the macules. Social and leisure activities are hampered due to the skin's appearance. [8,21] Patients believe that people focus on their skin rather than on what they are saying.[21]

Thus melasma greatly affects patients' quality of life.[5] The MELASQoL questionnaire is increasingly used to evaluate that impact.[6,8] It is important that that tool be adapted to the analyzed population's culture and language. The Brazilian version of MELASQoL has been validated, allowing the cultural identity to be preserved when using it in clinical and research activities.[8]

A number of studies have used the MELASQoL. In 2006, Cestari and colleagues conducted a study validating the MELASQoL-BP in a treatment with a fixed dose of a triple combination containing 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide. The average pre-treatment MELASQoL score was 44.4 (standard deviation, SD, ±14.9); after treatment, the average score dropped to 24.3 (SD 15.5), a statistically significant improvement ($p < 0.001$). For the item "annoyed most of the time" or "annoyed all of the time," there was a special focus on the factors "appearance of the skin before and after treatment" (decreasing from 69.8% to 10.1%), "frustration" (from 59.7% to 12.2%), "embarrassment" (from 56% to 9.3%) and "impact on relationships with other people" (from 35.3% to 5.8%).[8]

A 2008 study by Scherdin and others described that after eight weeks of treatment, MELASQoL decreased to 19.4 from 28.3 ($p < 0.001$), with the greatest improvement in the items "appearance of the skin" and "frustration and depression due to the skin's condition."[5] In 2008, Freitag published a sectional study evaluating the impact of melasma in the quality of life of 84 Brazilian women. The average MELASQoL-BP was 37.5 (SD ±15.2); the most affected aspects were related to the patients' emotional well-being (appearance, frustration, embarrassment and not feeling attractive).[6]

In line with the studies mentioned above, the MELASQoL items that presented the worst scores at the beginning of the present study were appearance, frustration, embarrassment and feeling less attractive. While both groups presented improvement in the present study, there were no statistically significant differences between the groups.

Hydroquinone is a phenolic agent structurally similar to the melanin precursors that, in addition to acting in the degradation of melanosomes, act upon melanocytes, possibly causing their necrosis. [3] After using hydroquinone for five to seven weeks, it is possible to note a considerable depigmentation. That treatment should last at least three months.[3] Hydroquinone is a primary irritant agent and can cause erythema and desquamation before the depigmentation takes place; those effects are proportional to the concentration employed.[24]

The botanical extract *belides*, extracted from *Bellis perennis* flowers, inhibits endothelin-1 and decreases the production of eumelanin in order to reduce the linking of α-MHS to its receptors. Regarding the melanin already that has already been produced, *belides* has a whitening effect when reducing the transfer of melanosomes from the melanocytes to the cells of the

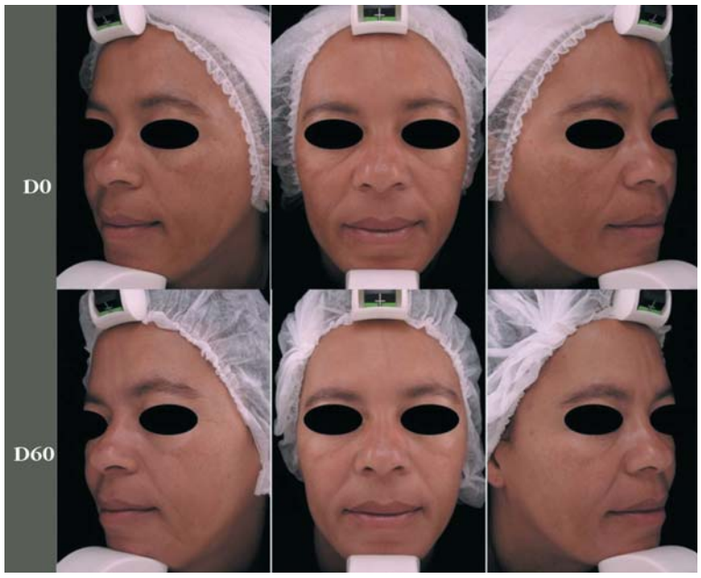

Figure 3: Group A volunteer before (Day 0) and after (Day 60) treatment

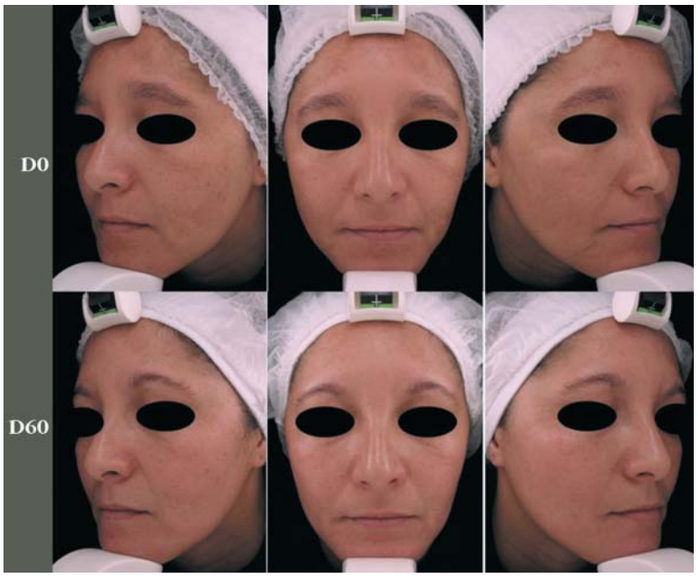

Figure 4: Group B volunteer before (Day 0) and after (Day 60) treatment

epidermis.[18] Liquorice, in turn, is extracted from the liquorice plant, named *Glycyrhiza glabr*a.[3] Its glabridin component inhibits tyrosinase without altering the synthesis of DNA. [3,20,25] Saponins and flavonoids are the active principles with the greatest anti-inflammatory properties. Liquiritin, also present in *Glycyrhiza glabr*a, has a melanin dispersing action, which results in depigmentation.[18] Liquiritin's efficacy suggests it can be an alternative to hydroquinone.[26] An additional extract is *emblica*, an active principle extracted from the *Phyllanthus emblica* fruit; its antioxidant mechanism moderately inhibits peroxidase and strongly inhibits the reaction of iron with peroxide. It also leads to the whitening of the skin when inhibiting tyrosinase.[18,19]

The depigmenting clinical benefits of botanical extracts *Bellis perennis*, *Glycyrrhiza glabra* and *Phyllanthus emblica*, compared to 2% hydroquinone, in patients with melasma were demonstrated in this study. [18] We found significant – and statistically similar – clinical improvement for both groups (Figures 1 and 2) (Graphs 1 and 2). Such improvement was detected by using the Melasma Area Severity Index (MASI) for a period of 60 days after the beginning of treatment. 18 The MASI scale (from 0 to 48) average score for the group that used botanical extracts was 10.9 (before treatment) and 5.7 (after treatment), meaning an improvement of 47.2%. For the hydroquinone group, MASI scores dropped from 10.2 to 4.4 after treatment (improvement of 57.3%). There was no statistically significant difference between the groups (p-value > 0.05).18 Average MASI scores range from 10-13 in most published studies.[6]

CONCLUSION

From those data, it is possible to note the importance of appreciating the quality of life of melasma patients and not treating that condition as only an aesthetic problem. Many patients forego treatment since melasma is a clinically benign disorder, although their psychological and emotional well-being is affected. The physician must weigh the benefits that the treatment will provide for the patient's life, as well as choose the best therapeutic option in each case. Therefore, the search for effective alternative treatments to hydroquinone must be considered and incentivized. In addition to providing depigmenting potential in the treatment of melasma, the use of botanical extracts of *Bellis perennis*, *Glycyrrhiza glabra* and *Phyllanthus emblica* improves the quality of life of patients with that dermatosis. ●

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