

Double-blind comparative study of hydroquinone and ursine grape extract in the treatment of melasma

Estudo duplo cego comparativo entre hidroquinona e extra-to de uva-ursina no tratamento do melasma

ABSTRACT

Introduction: Melasma is an acquired and progressive hyperpigmentation of photoexposed areas. For being a recurrent and refractory dermatosis, its treatment continues to be a challenge.

Objective: To evaluate the efficacy and security of the Skin Whitening Complex in the treatment of the facial melasma, and to compare it to the hydroquinone.

Materials and methods: Double-blind Comparative study of 13 women bearers of melasma. All received two different formulations, labelled as "right side of the face" and left "side of the face". The formulations were applied twice a day for 90 consecutive days. Only the pharmacist responsible for the formulations had knowledge of their content. The tests of Wilcoxon and χ^2 of McNemar-Bowker were employed in the statistical analysis.

Results: Ten of the 13 patients presented the global clinical improvement of the melasma. Four patients presented total improvement and six ($p = 0.004$) presented partial improvement in the hemiface treated with hydroquinone 4%. In the hemiface treated with Skin Whitening Complex 5%, the improvement was total in two patients, and partial in six ($p = 0.007$). There were no statistically significant differences between the two treatments ($p = 0.223$).

Conclusions: Although the treatment with hydroquinone 4% presents better clinical results, there were no statistically significant differences between the two treatments. Skin Whitening Complex 5% has shown efficient and safe in the treatment of the melasma.

Keywords: melanosis/therapy; hyperpigmentation; hidroquinones.

RESUMO

Introdução: Melasma é hiperpigmentação adquirida e progressiva em áreas fotoexpostas. Seu tratamento continua sendo um desafio por ser dermatose recorrente e refratária.

Objetivo: Avaliar a eficácia e segurança do Skin Whitening Complex no tratamento do melasma facial, e compará-lo à hidroquinona.

Pacientes e Métodos: Estudo duplo-cego comparativo com 13 mulheres portadoras de melasma. Todas receberam duas formulações diferentes, identificadas como "lado direito da face" e "lado esquerdo da face", que foram aplicadas duas vezes ao dia durante 90 dias consecutivos. Apenas o farmacêutico responsável tinha conhecimento do conteúdo. Para análise estatística foram realizados os testes de Wilcoxon e χ^2 de McNemar-Bowker.

Resultados: Das 13 pacientes, 10 apresentaram melhora clínica global do melasma. Na hemiface tratada com hidroquinona a 4%, a melhora foi total em quatro pacientes, e parcial em seis ($p = 0,004$). Na hemiface tratada com Skin Whitening Complex 5%, a melhora foi total em duas pacientes, e parcial em seis ($p = 0,007$). Não houve diferença estatisticamente significativa entre os dois tratamentos ($p = 0,223$).

Conclusões: Embora o tratamento com hidroquinona 4% apresente melhor resultado clínico, não houve diferença estatisticamente significativa entre os dois tratamentos. O SWC 5% mostrou-se eficiente e seguro no tratamento do melasma.

Palavras-chave: melanose/terapia; hiperpigmentação; hidroquinonas.

Original Article

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INTRODUCTION

Melasma is a common condition characterized by progressive macular hyperpigmentation – from light brown to gray – located in photoexposed areas of the body. It primarily occurs in the malar prominences, forehead, upper lip, nasal region, chin, neck, chest, and forearms. The lesions are usually well delimited and symmetrical. Although 90% of the patients are female,¹ men with a family history of melasma or intense exposure to sunlight may also develop this condition.² While its prevalence is not known, it is more frequent in sunny countries. It can occur in any race or phototype, yet it is more common in patients of Asian and Hispanic background, and those with Fitzpatrick phototypes IV and VI.^{3,4} Although its etiopathogeny is not completely known, multiple factors are involved, especially those associated with the hormonal influence of pregnancy, oral contraceptives, hormonal replacement therapy, ultraviolet radiation (UVA and UVB), genetic predisposition, phototoxic drugs, anticonvulsants and thyroid disorders.⁵⁻⁷ Melasma is clinically classified by area affected into center facial region (its most common form), malar, and mandibular. Histologically, it is classified into epidermal, dermal, or mixed, according to the location of the pigment.⁸

Melasma is a recurring condition that is often resistant to treatment. Topical and oral treatments aim to reduce melanin synthesis, to inhibit the formation of melanosomes, and to promote their degradation. Regardless of treatment, wide spectrum photoprotection is essential to prevent the formation of new melanin and to reduce the oxidation of the melanin that has already been produced. Hydroquinone is considered the most effective topical treatment option, yet it is not without its drawbacks. It cannot be used indefinitely, and has a number of adverse effects including allergic or irritant contact dermatitis, confetti-like hypopigmentation, post-inflammatory hyperpigmentation, nail discoloration, telangiectasias, epidermal atrophy, and ochronosis.⁹⁻¹¹ It is not suitable for use during pregnancy, as it falls into the U.S. Food and Drug Administration's (FDA) risk C category.

Due to the side effects of hydroquinone, it is important to examine the efficacy of other depigmenting products. Other topical treatments are described in the literature, such as vitamin C, which promotes the conversion of melanin into leuco melanin, can be used in the mildest cases; azelaic acid, a dicarboxylic acid that inhibits the production of tyrosinase (an enzyme that acts as a catalyst for the production of melanin) and does not affect normal melanocytes; chemical peels (Jessner's Solution, salicylic acid, glycolic acid, trichloroacetic acid TCA);¹² and arbutin, which reduces melanin synthesis by inhibiting the activity of tyrosinase.¹³

The Skin Whitening Complex (SWC) is a depigmenting compound that contains: ursine grape extract (which competes with tyrosinase); biofermented *Aspergillus* (which breaks the ionic copper, essential for the activity of the tyrosinase enzyme); grapefruit extract (rich in citric and malic acids, which has an exfoliating action); and rice extract (rich in oligosaccharides, which have a moisturizing function). The SWC is approved for

use in concentrations of 2 to 5%.¹⁴ This study evaluates the SWC's efficacy and safety and compares it with hydroquinone in the treatment of facial melasma.

METHODS

Study design

Prospective, comparative, and double-blind study comparing 5% SWC and 4% hydroquinone in the treatment of melasma in female patients. The ethical recommendations of the 2000 Declaration of Helsinki were observed in the study protocol.

Study population

Female patients with a clinical diagnosis of melasma, treated at the Corrective Dermatology Clinic of Santa Casa of Misericórdia in Rio de Janeiro (Professor Rubem David Azulay Institute of Dermatology), were selected for this study during the period March-July 2005. The inclusion criteria were: aged between 25 and 50, Fitzpatrick's phototype III to VI, with a clinically evident presence of melasma. The exclusion criteria were: treatment within the last six months, use of contraceptives, presence of endocrine conditions, allergy to hydroquinone, pregnancy, and lactation.

Methods

An individual file for annotations of the accomplished queries was filled in with the patients' information and evaluations of possible clinical effects and side effects, made by the research physician. Following a detailed explanation of the study, the patients signed a free and informed term of consent, being followed up every 15 days for three months, at the Santa Casa of Misericórdia of Rio de Janeiro's Corrective Dermatology Clinic. The dermatologic examination was carried out by the research physician, and photographs were taken by a professional photographer (Fujy S2 10.2 megapixels) in a studio, with consistent distance and lighting conditions. The evaluation criteria were clinical and photographic (standardized digital pictures with and without ultraviolet); the decrease in color intensity of the lesion was used as the improvement parameter. The degree of improvement in the color was based on the scale used by Torok and others,¹⁵ applied separately on the two sides of the face (Table 1). The Melasma Area Score Index (MASI) evaluation scale did not apply, because it assesses the full face, rather than each side of the face separately.

The degree of global improvement, assessed by the investigator before the study and after three months of treatment, was applied separately to each side of the face, according to the scale used by Torok and others¹⁵ (Table 2).

The observer physician assessed side effects such as erythema and desquamation using a scale of 0 to 10: light (1 to 3), moderate (4 to 6) and intense (above 7).

Treatment

The patients received two tubes, identified as "right side of

the face" and "left side of the face," containing gel creams manipulated by Dermatus Medical Cosmetics Ltda (RJ-Brazil). Only the responsible pharmacist had knowledge of the content of each tube. The patients were instructed to apply the specific products on each side of the face twice a day (morning and evening) and to use SPF 60 sunscreen lotion for three months. The use of any other topical or oral product was not allowed for the duration of the study.

Statistical analysis

Wilcoxon and X² of McNemar statistical tests were applied, according to the measurement scale of the variables. The established level of statistical significance was $p < 0.05$. The software SPSS (Statistical Package for the Social Sciences – version 13.0) was used to analyze the data.

RESULTS

Thirteen patients, with ages between 29 and 46 and phototypes III to VI, completed the study; 10 demonstrated improvement (Figures 1A and 1B). On the right side of the face, treated with 4% hydroquinone, the improvement was total in four patients (Figures 2A and 2B) – including a patient with phototype V – and partial in the other six (Figure 3) ($p = 0.004$). On the left side of the face, treated with 5% SWC, the improvement was total in two patients and partial in six (Figures

4A e 4B e 5A e 5B) ($p = 0.007$) (Table 3). The improvement can also be observed in the UV-filtered photograph (Figure 6). Only three patients did not present any degree of improvement in either side of the face. Two patients presented isolated improvement on only the side treated with hydroquinone (Figures 8A and 8B). No significant differences were observed between the two treatments ($p = 0.223$) (Table 4).

Side effects were not observed on the side of the face treated with SWC. however, two patients presented erythema and light desquamation on the side treated with hydroquinone, which did not hamper the continuity of the treatment. The patients' perception of the clinical and collateral effects of the treatments was aligned with the research physicians' analysis of clinical observations.

Chart 1 - Clinical evaluation scale	
Lesion type	
Intensity	
0	minimum or equivalent to the normal surrounding skin pigmentation
1	minor pigmentation
2	moderate pigmentation
3	intense pigmentation (lesion remarkably darker than the normal surrounding skin)

Chart 2 - Clinical improvement scale	
Descrição da lesão	
Grau de melhora	
0 (complete improvement)	absence of hyperpigmentation
1 (partial improvement)	little hyperpigmentation
2 (absence of improvement)	evident hyperpigmentation



Figure 1: A and B - Global clinical improvement of melasma in both sides of the face after three months of treatment



Figures 2 A and 2 B - Total clinical improvement of the right side of the face, treated with 4% hydroquinone



Figures 4 A and 4 B - Partial clinical improvement of the left side of the face, treated with 5% Skin Whitening Complex

DISCUSSION

While several depigmenting agents for the treatment of melasma are described in the specialized literature, there are only a few publications regarding SWC – a depigmenting complex that presents advantages such as a stabile formulation, the fact that it is not an irritant, and can be used in pregnant women. A randomized, controlled, double-blind study¹⁶ was conducted in 2003, with 30 women divided into two groups. Group 1 received 4% hydroquinone on one side of the face and a placebo on the other, while Group 2 received 5% SWC on one side of the face and a placebo on the other. After three months, there was global improvement of 72% in the treated



Figures 3 A and 3 B: Partial clinical improvement of the right side of the face, treated with 4% hydroquinone



Figures: 5 A and 5B - Partial clinical improvement of the left side of the face, treated with 5% Skin Whitening Complex

Table 1 - Clinical improvement index after treatment with hydroquinone and SWC

Side/treatment	Pigmentation after treatment	Total (%)		Pigmentation before treatment			Improvement index*	p-value **
				1=minor	2=moderate	3=intense		
Right/4% hydroquinone	0 (minimal)	4	(30,8)	0	3	1	54,5%	0,004
	1 (minor)	5	(38,5)	0	2	3		
	2 (moderate)	2	(15,4)	0	1	1		
	3 (intense)	2	(15,4)	0	0	2		
	Total (%)	13	(100)	0	6 (46,2)	7 (53,8)		
Left/5% SWC	0 (minimal)	2	(15,4)	2	0	0	27,3%	0,007
	1 (minor)	4	(30,8)	0	3	1		
	2 (moderate)	4	(30,8)	0	2	2		
	3 (intense)	3	(23,1)	0	0	3		
	Total (%)	13	(100)	2 (15,4)	5 (38,5)	6 (46,2)		

* Ratio between the number of degrees improved (shaded region) and total number of degrees of potential improvement before treatment

** Wilcoxon test's p-value

Table 2 - Comparative clinical improvement of melasma after the use of hydroquinone and SWC

		Left side results – 5% SWC			
		Total improvement	Total improvement	Total improvement	p-value *
Right side results – 4% hydroquinone	Total (%)				
Melhora total	4	(30,8)	1	3	0 0,223
Melhora parcial	6	(46,2)	1	3	2
Sem melhora	3	(23,1)	0	0	3
Total (%)	13	(100)	2 (15,4)	6 (46,2)	5 (38,5)

* McNemar-Bowker X2 test's p-value

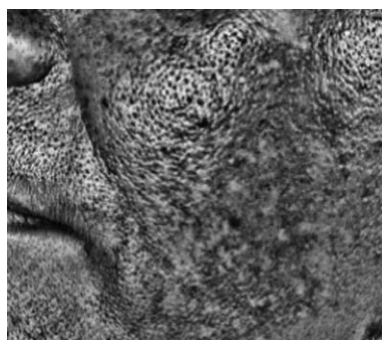


Figure 6 - Partial clinical improvement of the left side of the face, treated with Skin Whitening Complex 5%, observed under ultraviolet light

areas when compared to the placebo. In the hydroquinone group, 76.9% of patients presented improvement, with light adverse effects in 25%; 66.7% of patients in the SWC group presented improvement, with no adverse effects. There were no statistically significant differences between the groups ($p = 0.673$).

In this study, the two substances were applied to the same patient, and no placebo was used. The results obtained were similar to those described in the literature. The side treated with hydroquinone presented a better global result when compared to the side treated with SWC. However, SWC was not found to cause side effects, and between-group differences were not statistically significant.

CONCLUSION

Due to its long duration, it is often necessary to alternate depigmenting substances when treating melasma. Despite the availability of several depigmenters on the market, there are few studies that describe their efficacy and safety. The results presented in the present study show that, although treatment with hydroquinone produced better clinical results, there have

not been significant statistical differences between the two procedures, based on the sample size. Consequently, the SWC can be considered an alternative therapy, especially in patients that cannot use hydroquinone, including pregnant women. The

SWC can be considered an effective treatment for melasma, either by itself or in combination with other topical or oral substances. ●

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