Original Article

Double-blind randomized study of 5% and 10% retinoic acid peels in the treatment of melasma: clinical evaluation and impact on the quality of life

Estudo duplo-cego e randomizado do peeling de ácido retinoico a 5% e 10% no tratamento do melasma: avaliação clínica e impacto na qualidade de vida

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ABSTRACT

Introduction: Melasma is a highly prevalent dermatosis that greatly affects patients' quality of life and is challenging to treat. The Melasma Area and Severity Index and the Melasma Quality of Life Scale are useful tools in the clinical and impact on quality of life evaluations, respectively.

Objective: To compare the effects of 5% and 10% retinoic acid peels in patients with melasma, using the Melasma Area and Severity Index and the Melasma Quality of Life Scale to evaluate the clinical and quality of life impacts, respectively .

Methods: Patients (n = 30) were randomized to receive either 5% or 10% retinoic acid peels in weeks 0, 2, 4 and 6 of the treatment. Clinical and quality of life evaluations took place in weeks 0 and 8.

Results: In a global evaluation of the two groups, there was a statistically significant improvement in scores from baseline to week 8, yet there were no statistically significant differences between treatment groups.

Conclusions: Retinoic acid peels are effective and safe, as an isolated therapy, in the treatment of melasma. There is no difference in treatment results between 5% and 10% concentrations.

Keywords: melanosis; tretinoin; therapeutics; quality of life.

RESUMO

Introdução: *o melasma é dermatose de alta prevalência que provoca grande impacto na qualidade de vida dos pacientes. Seu tratamento é um desafio. O índice de área e gravidade do melasma – Masi, e o Melasma Quality of Life Scale – MelasQoL são instrumentos úteis na avaliação clínica e do impacto na qualidade de vida, respectivamente.*

Objetivo: *estudar, através do Masi e MelasQoL, o efeito do peeling de ácido retinoico em pacientes portadoras de melasma, comparando as concentrações de 5 e 10%.*

Métodos: *30 pacientes foram randomizados e submetidos a peelings de ácido retinoico a 5% ou 10% nas semanas 0, 2, 4 e 6. As pacientes foram submetidas à avaliação clínica, através do Masi e à avaliação da qualidade de vida, através do MelasQoL, nas semanas 0 e 8.*

Resultados: *na avaliação global dos dois grupos houve redução estatisticamente significativa de ambos os índices após os tratamentos. Quando se compararam os peelings de ácido retinoico a 5 e 10% não se observou diferença estatisticamente significativa entre as variáveis Masi e MelasQoL.*

Conclusões: *o peeling de ácido retinóico é eficaz e seguro no tratamento do melasma, como tratamento isolado, e não há diferença da melhora quando se comparam as concentrações de 5% e 10%.*

Palavras-chave: *melanose; tretinoína; terapêutica; qualidade de vida.*

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INTRODUÇÃO

Melasma is a high prevalence benign dermatosis that causes great impact in the patients' quality of life, interfering in many aspects of the psychosocial , family and professional life. [1] The difficult treatment, combined to a great demand for new treatments, propels the execution of clinical and pharmaceutic research.

The knowledge about its physiopathogeny is still limited. It is an acquired chronic hypermelanosis resulting from the focal hyperactivity of hyperfunctioning epidermal melanocytes clones. [2-4]

It is clinically characterized by hyperchromic macules in photoexposed areas, preferentially located in the frontal and malar regions. It is more frequent in women who live in areas with high ultraviolet radiation (UVR) indices and who in their fertile period and have high phototypes. The starting age is usually between 30 and 55, with male patients in around 10% of the cases.[1,5,6]

There is a great number of described etiopathogenic factors, among them: genetic influence, exposure to UVR, pregnancy, hormonal therapies, cosmetics, phototoxic substances, endocrinopathies, and vascular and emotional factors.[7-9]

The histopathological characteristics are not completely defined 10. Variable hyperpigmentation of the epidermis and increase of dermal elastosis are verified in the area affected by the melasma.[11,12] This happens due to an increase in the number of melanocytes with great melanogenic activity, superposed on dermal alterations caused by the solar radiation.

The treatment of the melasma is challenging for this dermatosis frequently presents a refractory and recurrent course 13. Chemical peelings are among the alternatives belonging in the therapeutic armamentarium 14 -16, with 1 to 10% retinoic acid peeling being an option. Several action mechanisms related to the retinoic acid are described: dispersion of the pigment granules in the keratinocytes, interference in the transfer of the melanosomes and increase in the speed of the cellular turnover, resulting in the increase in the loss of pigment.[7] Additionally, there is evidence that it can inhibit the tyrosinase production and the melanogenesis. [8]

There are few studies on retinoic acid peelings in the literature. Cucé et al. studied the clinical and histopathological modifications after serial tretinoin peelings in 1 to 5% concentrations, applied twice a week, having observed good results in several pathologies, including the melasma.[17] Khunger et al. compared the efficacy of the 1% retinoic acid peeling to that of the 70% glycolic acid, in 10 patients with high phototypes who received 12 weekly applications. No statistical difference was observed in the two treatments efficacy, with a significant decrease observed in the MASI (Melasma Area and Severity Index)18. In a recent study, Ghersetich et al. evaluated the efficacy of the 10% tretinoin peeling in 20 women, having observed an accentuated improvement of the melasma, with great tolerability and efficacy, without adverse effects.[19]

The MASI, described by Kimbrough-Green in 1994, is a useful tool in the clinical evaluation of the melasma. In its calculation, four areas of the face – frontal (F), right malar (RM), left malar (LM) and mentonian (M) are evaluated. The first three areas correspond to 30% of the total area of the face each, while the mentonian region, to 10%. Scores from 0 to 6 are attributed for each area, according to the melasma extension. The severity is measured by two factors: pigmentation (P) and homogeneity (H), in a scale of 0 to 4. The formula used is: MASI = 0.3 (PF + HF) AF + 0.3 (PRM + HRM) ARM + 0.3 (PLM + HLM) ALM + 0.1 (PM + HM) AM. The MASI final score ranges from 0 to 48.[20]

MELASQoL (Melasma Quality of Life Scale), published by Balkrishnan et al. in 2003, [21] is a tool used to quantify the quality of life linked to the health of women bearers of melasma. This tool was validated and demonstrated to be able to objectively evaluate melasma's impact on the patients' quality of life. The main sectors shown to be affected by the melasma were the social life, recreation/leisure and emotional well-being. In 2006, MELASQoL was translated into Portuguese language and culturally adapted. [22]

This paper was aimed at studying the effect of the retinoic acid peeling in melasma patients through MASI and MELASQoL. The intention was specifically to describe clinical and epidemiological aspects; to evaluate the retinoic acid peeling's therapeutic efficacy in the improvement of the melasma, carrying out a blind and randomized comparison of the 5% and 10% concentrations, correlating the resulting data to the improvement in quality of life, measured through MELASQoL (Portuguese language version).

METHODS

An experimental, prospective, double-blind and randomized study was carried out at the Cosmiatry outpatient ambulatory of the Dermatologic Clinic of the Santa Casa de Belo Horizonte, Minas Gerais State, Brazil, in melasma bearer outpatients, from January to May 2010.

Thirty patients were included in the study. The study was approved by the Research Ethics Committee, with all participants signing a term of free and informed consent. The inclusion criteria were: patients bearer of facial melasma (women or men); age above 18; Fitzpatrick scale phototypes from I to V and the signature of the term of free and informed consent.

The exclusion criteria were: pregnancy, lactation or planning to become pregnant in the next three months; patients bearers of other facial cutaneous disorders; known allergy to retinoic acid or the vehicle; use of topical medications (retinoids, hydroquinone, glycolic acid, etc), having undergone phototherapy or artificial tanning less than two weeks before; laser, IPL (intense pulsed light), dermabrasion or peeling treatment less than three months before; use of oral corticotherapy less than one month before; use of systemic retinoids, cyclosporin, interferon or methotrexate less than four months before; use of photoallergic, phototoxic or

photosensitizing substances less than one month before and use of hormonal replacement therapy less than one month before (except for continuous use for more than three months).

The patients were randomized, undergoing 5% or 10% retinoic acid peelings according to the group to which they were allocated in weeks 0, 2, 4 and 6, with the retinoic acid concentration being kept constant for a same patient. The application technique consisted in removing the skin's oiliness with a gauze with 3% acetone in alcohol, with the subsequent application of the product with a swab. The peeling presents a yellowish coloration, making easy to visualize an homogeneous application in all over the face. Patients were oriented to wash the face completely, removing the product 6 hours after the application. The single complementary treatment allowed was the use of photoprotector.

The patients underwent the clinical and quality of life evaluations through MASI and MELASQoL, respectively, in weeks 0 and 8.

A descriptive analysis of all variables was made at the beginning of the study. Tables of frequency distributions were elaborated for the nominal or categorical variables. Measures of central tendency (mean and median) and variability (standard deviation, minimum and maximum) were calculated for the continuous variables. The t-paired test was used to compare MASI and MELASQoL scales values before and after the treatment. A variable representing the difference between initial and final values of the two scales was created aiming at quantifying the magnitude of the reduction in the scores after the treatment. Subsequently, the factors associated to that difference in the values were analyzed through Student t- tests and ANOVA or Pearson correlation coefficient (in the case of the continuous variables). The choice for parametric tests in all analyses was due to the symmetrical character of the continuous variables analyzed. The significance level for acceptance was set at 5%. The SPSS 15.0 was the used software.

RESULTS

The ages of the patients studied ranged from 25 to 59 (mean of 41.4). Of the 30 patients included in the study, 90% (27 patients) were women and 10% (3 patients) men. The most prevalent phototype was IV (50%) followed by phototype III (36.7%). All patients lived in urban areas and 73.3% had never smoked (Table 1).

It can be observed in table 2 that only 10% of the patients described some previous dermatologic disorder (acne, allergic contact dermatitis and atopic dermatitis). At the beginning of the study, 4 patients (13.3%) presented other dermatologic disorders (vitiligo, alopecia areata, tinea corporis, and contact dermatitis).[9] patients stated to have systemic disorders when asked about co-morbidities. The most prevalent disorder was hypertension (5 patients), followed by hypothyroidism (2 patients) and epilepsy; urinary incontinence and mamma neoplasia (each with one patient).

Observing table 3 we conclude that 80% of the patients had previous history of use of some systemic medication, including contraceptives, antihypertensive, anticonvulsant etc.

Table 1: Epidemiologic profile of studied patients – origin, phototype, tabagism, gender (n=30)

	Frequency	%
Origin		
Rural	0	0
Urban	30	100
Phototype		
II	1	3,3
III	11	36,7
IV	15	50
V	3	10
Tabagism		
Active	2	6,7
Ex-smoker	6	20
Never smoked	22	73,3
Sexo		
Female	27	90
Male	3	10

Table 2: Epidemiologic profile of studied patients –previous and active skin condition, systemic disorders (n=30)

	Frequency	%
Previous skin condition		
Which?		
Acne	3	10
Contact dermatitis	1	3,3
Allergic dermatitis	1	3,3
Atopic dermatitis	1	3,3
Active skin condition		
Which?		
Allergy	4	13,3
Alopecia areata	1	3,3
Tinea corporis	1	3,3
Tinea corporis	1	3,3
Vitiligo	1	3,3
Systemic disorders*		
Which?		
Epilepsy	9	31
Arterial hypertension	1	3,3
Systemic hypertension	5	16,7
Hypotiroidism	2	6,7
Urinary incontinence	1	3,3
Mamma neoplasia	1	3,3

*n=29

Only 20% of the patients described the existence of some relationship between the use of those medications with the emergence of the melasma. At the time of the study, 5 patients were using hormonal contraceptives or hormonal replacement therapies. The duration of the use of those medications ranged from 7 months to 17 years.

Table 3: Epidemiologic profile of studied patients – medicament use history and relationship with the beginning of melasma (n=30)

	Frequency	%
History of systemic medicament use		
Yes	24	80
No	6	20
Relationship with the beginning of melasma*		
Yes	6	20
No	23	76.7
Current use of oral contraceptive/hormonal replacement therapy*		
Yes	5	16.7
No	24	80

*n=29

Table 4: Epidemiologic profile of studied patients – relationship of melasma patches to pregnancy and use of sunscreen (n=30)

	Frequency	%
Patches appeared or worsened during pregnancy		
Yes	11	36.7
No	8	26.7
n.a.*	11	36.7
Use of sunscreen		
Yes	27	90
No	3	10
Number of daily applications**		
1	3	10
2	14	46.7
3	8	26.7
4	2	6.7

* Patients who have never got pregnant (including male patients)
**n = 27

Eleven patients (36.7%) described the appearance or aggravation of melasma macules during pregnancy. When questioned about the use of suntan lotions, 90% stated that they used the product, and almost half applied the product twice daily (Table 4).

From the initial group of 30 patients, 28 (14 in each group) completed the study, having their MASI and MELASQoL values analyzed. Regarding the two excluded patients, one underwent 2 retinoic acid peelings and the other 3. Both manifested the desire to interrupt the participation in the study due to local irritation, which no longer was evident at the moment they returned for clinical evaluation. The mean value of MASI in the beginning and at the end of the treatment were 13.4 and 7.7 ($p < 0.01$), respectively. For the MELASQoL, the initial and final values were 37.6 and 30.9 ($p=0.02$), respectively. Statistically significant difference was found in MASI and MELASQoL values when we compared the two moments, as shown in Table 5. When comparing initial and final values of MASI and MELASQoL, stratified according the type of peeling used (5 or 10%), the statistically significant difference remains only for the MASI (Tables 6 and 7). The two groups presented $p < 0.01$ being, therefore, statistically similar in spite of the greater difference between initial and final mean values TO have occurred in patients belonging in the 5% peeling group.

There was no statistically significant difference between 5% and 10% retinoic acid peelings regarding the MASI and MELASQoL variables (Table 8).

The following variables were analyzed in the study of the MASI and MELASQoL initial and final scores: phototype, previous or active skin disorder, presence of systemic disorder, use of systemic medications and its time relationship with the appearance of the melasma, current use of hormonal contraceptive or hormonal replacement therapy, tabagism, age of the menarche and menopause. The only factor that presented a statistically significant association with the difference in the MASI scale scores was the current use of oral contraceptive or hormonal replacement therapy: the patients who were not using

Table 5: Comparison between MASI and MELASQoL scales before and after the peelings (n=28)

MASI/ MELASQoL	Mean	Standard deviation	P Value
Initial MASI	13.4	7.3	
Final MASI	7.7	5.6	
Initial MASI – final MASI	5.7	3.7	<0.001
Initial MELASQoL	37.6	15.9	
Final MELASQoL	30.9	15.7	
Initial MELASQoL - final MELASQoL	6.7	14.4	0.02

Table 6: Comparison between MASI and MELASQoL scales before and after 5% retinoic acid peelings (n=14)

Masi/MelasQoL	Média	Desvio-padrão	Valor p
Initial MASI	15.6	8.5	
Final MASI	8.9	7.0	
Initial MASI – final MASI	6.7	3.9	<0.001
Initial MELASQoL	34.3	13.8	
Final MELASQoL	30.1	12.4	
Initial MELASQoL - final MELASQoL	4.2	11.1	0.177

Table 7: Comparison between MASI and MELASQoL scales before and after 10% retinoic acid peelings (n=14)

MASI/ MELASQoL	Mean	Standard deviation	P Value
Initial MASI	11.1	5.12	
Final MASI	6.4	3.5	
Initial MASI – final MASI	4.7	3.3	<0.001
Initial MELASQoL	40.9	17.7	
Final MELASQoL	31.4	19.0	
Initial MELASQoL - final MELASQoL	9.2	17.1	0.065

Tabela 8 – Comparação das diferenças das escalas Masi e MelasQoL antes e após os *peelings* de ácido retinoico 5 e 10%

	MASI initial - Masi final 5%	MASI initial - MASI final 10%	MelasQoL final - MelasQoL initial 5%	MelasQoL initial - MelasQoL final 10%
Mean	6.7	4.7	4.2	9.2
P Value	0.726		0.09	

those medications presented greater reduction in MASI scores (p=0.049). None of the variables presented difference regarding the initial and final MELASQoL scores.

Considering the safety of the 5 and 10% retinoic acid peelings, few adverse effects, such as erythema and transitory desquamation in the immediate post-peeling were observed.

DISCUSSION AND CONCLUSION

The study population had an average age of 41.4, with the prevalence of the phototype IV (50%). 31% of the studied patients presented some systemic disorder, with hypertension (16.6%) and hypothyroidism (6.6%) being the most frequent. 80% of the patients presented previous history of use of some systemic medication, and only 25% described some relationship between the use of those medications with the beginning/appearance of the melasma. 36.7% of the patients described the appearance or aggravation of the macules during pregnancy. Such data confirm the prevalence of this dermatosis in higher phototypes and reinforce the variability of the etiopathogenic factors.

Another interesting finding is that 90% of the sample studied made regular use of photoprotector, with almost 50% of this group applying the product twice a day.

Two patients did not complete the study, both motivated by mild adverse effects in the immediate post-peeling.

In a global evaluation of the two groups, there was a statistically significant reduction of MASI and MELASQoL before and after the treatments. The average decreases of MASI and MELASQoL were 6.7 ($p < 0.01$) and 5.7 (p=0.02), respectively, meaning that both the 5% and the 10% retinoic acid peelings were effective as an isolated treatment of the melasma.

The difference between initial and final MASI for the 5% peeling group was 6.7 ($p < 0.01$), while for the MELASQoL that figure was only 4.2 (p=0.177). The same was found for the 10% peeling group: a difference between initial and final MASI and MELASQoL of 4.7 ($p < 0.01$) and 9.2 (p=0.065), respectively. It is possible to conclude, therefore, that both peelings, when evaluated separately, are capable of producing clinical improvement – which does not correspond to a proportional improvement in the quality of life.

When 5% and 10% retinoic acid peelings are compared, no statistically significant difference can be observed regarding the MASI and MELASQoL variables.

A number of variables were analyzed regarding the initial and final MASI and MELASQoL scores: no variable presented difference in the initial and final MELASQoLs; regarding the difference in the MASI scale scores, the only factor that presented statistically significant association was the current use of oral contraceptive or of hormonal replacement therapy, being worth to note that patients who were not using those medications presented a greater reduction in MASI scores (p=0.049).

Chemical peelings can contribute in the treatment of melasma,[16] however much is discussed on the lack of well controlled and replicable studies on the subject.[14] Furthermore, few clinical studies on the effect of retinoic acid peelings in the treatment of melasma were carried out. Ghersetich et al. evaluated the efficacy of 10% tretinoin peeling in 20 women, observing an improvement in the melasma, with great tolerability and no adverse effects.[19] Khunger et al. compared the 1% retinoic acid and 70%glycolic acid peelings in 10 patients with high phototype, in 12 weekly applications without observing statistical difference between the efficacy of the two treatments, except for a significant decrease in the MASI.[18]

Another interesting fact was the occurrence of few adverse effects in a group of patients with high phototype (IV in 50% of the patients), evidencing the high safety level of this peeling. All effects, such as erythema and desquamation, were mild and transient, taking place in the immediate post-peeling.

It can be inferred that retinoic acid peeling is effective and safe in the treatment of the melasma as an isolated treatment, with no difference in the improvement of the condition when 5% and 10% concentrations are compared.

The authors suggest that additional studies be carried out to investigate lower retinoic acid concentrations and compare that substance to other superficial peelings. ●

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REFERENCES

1. Miot LDB, Miot HA, Silva MG, Marques MEA. Physiopathology of melasma. An Bras Dermatol. 2009; 84(6):623-35.
2. Miot LDB, Miot HA, Silva MG, Marques MEA. Estudo comparativo morfo-funcional de melanócitos em lesões de melasma. An Bras Dermatol. 2007; 82(6): 529-64.
3. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. J Cosmet Dermatol. 2007; 6(3):195-202.
4. Grimes P, Nordlund JJ, Pandya AG, Taylor S, Rendon M, Ortonne JP. Increasing our understanding of pigmentary disorders. J Am Acad Dermatol. 2006; 54 (5 Suppl 2): S255-61.
5. Steiner D, Feola C, Bialeski N, Silva FAM. Tratamento do melasma: revisão sistêmica. Surg Cosmet Dermatol.2009;1(1):87-94.
6. Grimes PE. Melasma. Etiologic and therapeutic considerations. Arch Dermatol. 1995; 131(12):1453-7.
7. Hassun, KM; Bagatin, E; Ventura, KF. Melasma. RBM rev bras. 2008; 65:11-16.
8. Rendon M, Berneburg M, Arellano I, Picardo M. Treatment of melasma. J Am Acad Dermatol. 2006; 54(5 suppl 2):S272-81.
9. Pandya A, Berneburg M, Ortonne JP, Picardo M. Guidelines for clinical trials in melasma. Pigmentation Disorders Academy. Br J Dermatol. 2006;156 (Suppl 1): 21-8.
10. Kang WH, Yoon KH, Lee ES, Kim J, Lee KB, Yim H, et al. Melasma: histopathological characteristics in 56 Korean patients. Br J Dermatol. 2002;146(2):228-37.
11. Ponzio HAS. Contribuição à classificação clínica e histopatológica dos melasma [dissertação]. Porto Alegre: UFRGS; 1995. p. 157.
12. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL,Mihm Jr MC. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol. 1981;4(6):698-710.
13. Aditya K, Gupta MD, Gover MD, Nouri K,Taylor S. The treatment of melasma: A review of clinical trials. J Am Acad Dermatol, 2006 55(6):1048-65.
14. Bagatin E, Hassun K,Talarico S. Revisão sistêmica sobre peelings químicos. Surg Cosmet Dermatol. 2009; 1(1):37-46.
15. Magalhães GM, Borges MFB, Oliveira PJV, Neves DR. Peeling de ácido láctico no tratamento do melasma: avaliação clínica e impacto na qualidade de vida. Surg Cosmet Dermatol. 2010; 2(3):173-9.
16. Steiner D, Feola C, Bialeski N, Silva FAM, Antiori ACP, Addor FAZ, et al. Estudo de avaliação da eficácia do ácido tranexâmico tópico e injetável no tratamento do melasma. Surg Cosmet Dermatol. 2009;1(4):174-7.
17. Cucé LC, Bertino MCM, Scattone L, Birkenhauer MC. Tretinoin Peeling. Dermatol Surg. 2001;27(1):12-4.
18. Khunger N, Sarkar R, Jain RK. Tretinoin Peels versus Glycolic Acid Peels in the Treatment of Melasma in Dark-Skinned Patients. Dermatol Surg. 2004;30(5): 756-60.
19. Ghersetich I, Troiano M, Brazzini B, Arunachalam M, Lotti T. Melasma: treatment with 10% tretinoin peeling mask. J Cosmet Dermatol. 2010; 9(2):117-21.
20. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, et al. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. Arch Dermatol. 1994;130(6):727-33.
21. Balkrishnan R, McMichael AJ, Camacho FT, Saltzberg F, Housman TS, Grummer S ,et al. Development and validation of health-related quality of life instrument for women with melasma. Br J Dermatol. 2003;149(3):572-7.
22. Cestari TF, Hexsel D, Viegas ML, Azulay L, Hassun K, Almeida AR, et al. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. Br J Dermatol. 2006;156 (Suppl 1):13-20.