INVESTIGATION

Efficacy of topical combination of benzoyl peroxide 5% and clindamycin 1% for the treatment of progressive macular hypomelanosis: a randomized, double-blind, placebo-controlled trial *

Eficácia da combinação tópica de peróxido de benzoíla 5% e clindamicina 1% para o tratamento da hipomelanose macular progressiva: um estudo randomizado, duplo-cego, placebo-controlado

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Abstract: BACKGROUND: Progressive macular hypomelanosis is a dermatosis without definite etiology. There is no consensus or first-line therapy in the treatment of progressive macular hypomelanosis, and the treatment options used are very little effective.
OBJECTIVE: To evaluate the therapeutic efficacy of the topical combination of benzoyl peroxide 5% and clindamycin 1% associated with sun exposure for the treatment of progressive macular hypomelanosis.
MATERIALS AND METHODS: This is a randomized, double-blind, placebo-controlled study in which patients were divided into two groups. Group A used the topical combination of benzoyl peroxide 5% and clindamycin 1% and Group B used gel cream as a placebo. Patients were advised to expose themselves to the sun on a daily basis and were systematically evaluated and photographed. The collected data were entered and analyzed using Epi Info. A p value < 0.05 was considered statistically significant.
RESULTS: Out of the 23 patients included in the study, 13 were in group A and 10 in group B. Eleven patients (85%) in group A had significant clinical improvement and only two patients (20%) in group B showed an equivalent clinical improvement ($p = 0.003$). Side effects were more frequent in group A ($p = 0.003$).
CONCLUSION: The topical combination of benzoyl peroxide 5% and clindamycin 1% is effective in the treatment of progressive macular hypomelanosis.
Keywords: Benzoyl Peroxide; Clindamycin; Skin diseases

Resumo: FUNDAMENTOS: A hipomelanose macular progressiva é uma dermatose sem etiologia definida. Não há consenso ou medicação de primeira linha para o seu tratamento e os tratamentos utilizados são pouco eficazes.
OBJETIVO: Avaliar a eficácia terapêutica da combinação tópica de peróxido de benzoíla 5% e clindamicina 1% associada à exposição solar para o tratamento da hipomelanose macular progressiva.
MATERIAIS E MÉTODOS: Trata-se de um estudo randomizado, duplo-cego, placebo-controlado, no qual os pacientes foram divididos em dois grupos: o Grupo A utilizou a combinação tópica de peróxido de benzoíla 5% e clindamicina 1% e o Grupo B usou um creme gel como placebo. Os pacientes foram orientados à exposição solar diária, avaliados e fotografados sistematicamente. Os dados coletados foram inseridos e analisados pelo software Epi Info. Definiu-se a significância estatística por valor de $p<0,05$.
RESULTADOS: Dos 23 pacientes incluídos, 13 foram do Grupo A e 10, do Grupo B. Onze pacientes do primeiro grupo (85%) obtiveram melhora clínica importante e apenas dois (20%) do segundo grupo obtiveram uma melhora clínica equivalente ($p=0,003$). Os efeitos colaterais foram mais frequentes nos pacientes do Grupo A ($p=0,003$).
CONCLUSÃO: A combinação tópica de peróxido de benzoíla 5% e clindamicina 1% é eficaz no tratamento da hipomelanose macular progressiva.
Palavras-chave: Clindamicina; Dermatopatias; Peróxido de benzoíla

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INTRODUCTION

Progressive macular hypomelanosis (PMH) is a dermatosis characterized by nummular, hypopigmented, symmetric, asymptomatic macules of unclear etiology which affect the front and back of the trunk and are confluent around the midline. It occurs in all races and has a worldwide distribution but is more frequently identified in black people or in people originating from tropical countries, young adults and women. [1-4] The diagnosis is clinical and the main differential diagnoses are pityriasis versicolor and pityriasis alba. [3-5]

Guillet *et al* (1988) suggested that PMH is a disease of racial character that affects people of mixed races. This hypothesis was based on observations of ultrastructural findings that revealed single melanosomes (negroid) and aggregated melanosomes (caucasoid) responsible for variations in skin tone. [2] Histological observation of moderate perifollicular lymphocytic infiltrate in the lesion also suggests that the hypopigmentation of the skin may be secondary to an inflammatory process; however, there are no clinical signs of inflammation in PMH. [1,4]

In 2004, Westerhof *et al.* proposed that colonization by *Propionibacterium acnes* may be involved in the pathogenesis of PMH. This finding was based on the observation of red follicular fluorescence in the hypopigmented spots, which was absent in adjacent normal skin, when examined under a Wood's light in a dark room.The presence of positive culture of the pilosebaceous duct of the skin lesion also ratified this hypothesis. *P. acnes* produces a substance that interferes with the production of melanin, causing hypopigmentation of the skin. [1,4]

Various therapy options have been used with variable results for the treatment of PMH, including local hydration, sun exposure, phototherapy, topical corticosteroids and oral tetracycline.[4] However, there is no first-line medication or consensus in the treatment of this dermatosis and the treatment options used have shown to be not very effective. [4] The combination of benzoyl peroxide 5% and clindamycin 1% is quite effective against *P. acnes.* Clindamycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, whereas benzoyl peroxide has free radicals that produce oxygen molecules that react with the bacterial cell wall, eliminating the *P. acnes.* Moreover, the combined use of benzoyl peroxide with topical antibiotic reduces the risk of development of resistant *P. Acnes.*[6] Elimination of *P. acnes* with a topical antimicrobial therapy could improve repigmentation in patients with PMH.[1]

The aim of this study was to evaluate the therapeutic efficacy of the topical combination of benzoyl peroxide 5% and clindamycin 1% associated with sun exposure for the treatment of progressive macular hypomelanosis.

MATERIALS AND METHODS

This study was conducted at the outpatient dermatology service of Santa Izabel Hospital, Salvador-Bahia. Criteria for inclusion were: older than 15, clinical diagnosis of PMH confirmed by two dermatologists, negative direct mycological examination and no previous treatment for more than 30 days. Pregnant or lactating women, patients with associated diseases and patients allergic to the therapy drugs used in the study or sensitive to sunlight were excluded. This study was previously submitted to and approved by the local research ethics, and an informed consent form was signed by all patients.

This is a randomized, double-blind, placebo-controlled, pilot study. The patients were divided into two groups. Group A received a combination of topical benzoyl peroxide 5% and clindamycin 1% and Group B received a gel cream placebo. The medication vehicle used in both groups was identical gel cream. The drugs formulated were placed in equal tubes and named A and B. Randomization was previously performed at random through a randomization table, and patients and doctors did not know about the allocation of patients in the groups. The patients were instructed on the application of medication and advised to expose themselves to the sun for 20 minutes on a daily basis. The drugs were used for three months. The patients were evaluated and photographed by the same investigators on days 0, 15, 60 and 90 after beginning the treatment. Cure criterion was based on clinical evaluation performed by two examiners and on a photograph analysis. The following scale of clinical improvement was previously established based on the area of repigmentation: no improvement, little improvement, partial improvement, significant improvement and complete recovery.

The collected data were entered and analyzed in *Epi* Info version 3.5. The statistical tests used were the *Shapiro-Wilk* test, to verify if the patients' age and duration of illness had a normal distribution, the *Kruskal-Wallis* test, *to* compare if there were statistically significant differences between the medians, and *Fisher's* exact test, to verify if the patients showed clinical improvement. Results were considered statistically significant if the p value was less than 0.05.

RESULTS

The study was conducted from October 2008 to April 2009. 23 patients were included in the study, 13 in group A and 10 in group B. Of the 23 patients evaluated, 20 (87%) were female and 3 (13%) were male. Their age ranged from 18 to 67, with a median age of 25 and quartiles of 21 and 35. Disease duration ranged between 0.08 and 50 years, with a median of two years and quartiles of one and seven years. Sex, age and duration of the disease were similar in both groups (Table 1). All of the patients examined had lesions on the back and 16 (70%) of the patients also had lesions in the abdomen. Less common parts such as breasts, buttocks and limbs were also affected.

All patients reported taking the medication regularly, but only seven patients (30%) reported having daily sun exposure of the lesions, four patients (57%) from group A and three (43%) from group B. Eleven patients (85%) in group A showed significant improvement of lesions and only two patients (20%) in group B showed equivalent clinical improvement, with a statistically significant difference between the two groups, p = 0.003 (Figures 1, 2, 3 and 4). Seven patients (53%) in group A showed complete recovery of lesions after 90 days after beginning the therapy and only two patients (20%) in group B were cured at the same time interval.

Thirteen patients (56%) had at least one side effect during treatment, eleven (85%) patients from group A and two (15%) from group B, with a statistically significant difference between the two groups (p = 0.003). The clinical side effects reported were pruritus (50%), stinging (40%), erythema (30%), desquamation (22%), burning sensation (22%), xeroderma (8%) and plaques (4%). The side effects were well tolerated by all patients and there was no loss in terms of follow-up.

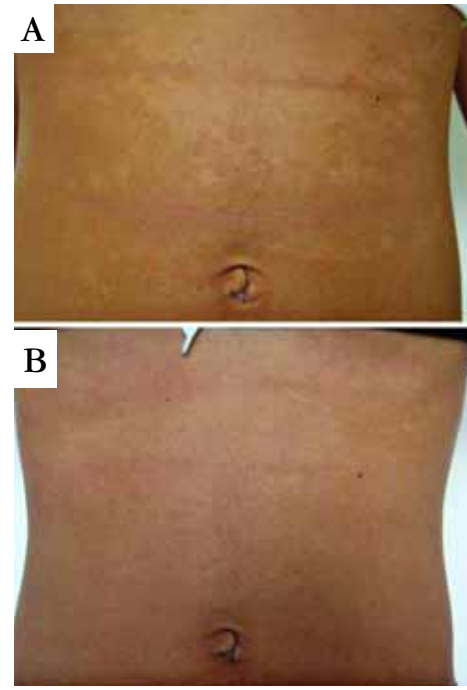

Figure 1: A - Group A patient: female, 19 years old, before treatment; **B -** Group A patient: female, 19 years old, on the 90th day of treatment, with significant improvement of lesions

DISCUSSION

This study shows that the use of the topical combination of benzoyl peroxide 5% and clindamycin 1% improves hypopigmentation in PMH. Demographic differences between the two groups were not significant. Despite the prevalence of women in this study, there are no reports in the literature showing that gender influences the response to treatment against *P. acnes.* Patient adherence to regular sun exposure was similar between the two groups, which excludes the possibility of solar radiation being the main factor responsible for treatment success. It is possible that

Table 1: Demographic data of the patients evaluated

	Peroxide + Clindamycin	Placebo	p
Age (years old)			
Median	30 (23-35)	24 (19-31)	0,4[a]
Variation	18-67	19-37	
Sex (%)			
Male	15,4	10	0,6[b]
Female	84,6	90	
Disease duration (years)			
Median	4 (1-10)	1,25 (0,5-2)	0,1[a]
Variation	0,08-50	0,08-20	

[a] Kruskal-Wallis test
[b] Fisher's exact test

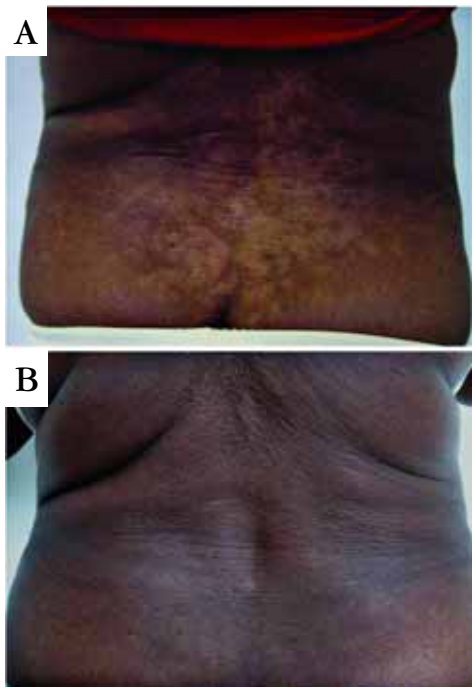

Figure 2: A – Group A patient: female, 67 years old, before treatment; **B -** Group A patient: female, 67 years old, on the 90th day of treatment, with complete recovery of lesions

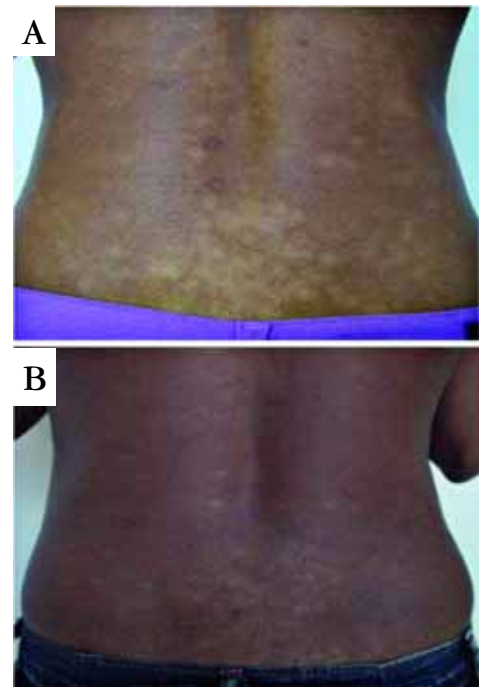

Figure 4: A – Group B patient: female, 19 years old, before treatment; **B -** Group B patient: female, 19 years old, on the 90th day of treatment, with partial improvement of lesions

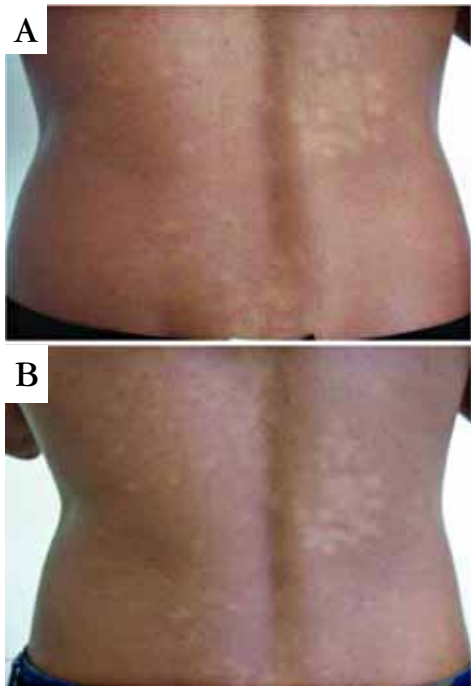

Figura 3: A – Group B patient: female, 19 years old, before treatment; **B -** Group B patient: female, 19 years old, on the 90th day of treatment, no improvement of lesions

sun exposure accelerates repigmentation after antibacterial treatment. [3]

The choice of the antimicrobial was due to the fact that the combination of benzoyl peroxide 5% and clindamycin 1% is very effective against *P. acne,* [6] easy to apply and has few side effects. [6] Even though reports of side effects were significantly higher in the group treated with the antimicrobial, there was no treatment dropout as a result.

The main limitations of this study were small sample size, follow-up duration and absence of confirmation of *P. acnes. P. acnes* was not objectively demonstrated in the lesions, but the significant clinical improvement of the group treated with benzoyl peroxide 5% and clindamycin 1% suggests colonization and supports the hypothesis that colonization by *P. acnes* may be involved in the pathogenesis of PMH. [1]

Randomized, double-blind, placebo-controlled clinical trials are described as a gold standard test in the evaluation of therapeutic issues for reducing the likelihood of obtaining biased data in research. [7] Even though PMH is a very common hypochromic dermatosis in our environment, there are no double-blind, placebo-controlled studies published in the literature that demonstrate the efficacy of antimicrobials in the treatment of PMH.

While PMH is not a serious disease, it is an unaesthetic dermatosis, little studied in the literature and with no established standard treatment. [4] The results of the response profile of patients treated with the topical combination of benzoyl peroxide 5% and clindamycin 1% associated with sun exposure can be used in clinical practice as a therapeutic alternative for the treatment of PMH.

The future perspective is to evaluate the patients treated in order to assess rate of relapse and time of remission after treatment.

CONCLUSION

The combination of benzoyl peroxide 5% and clindamycin 1% is effective in the treatment of PMH. Furthermore, the results of this study corroborate the hypothesis that skin colonization by *P. acnes* may be involved in the pathogenesis of the disease. ❑

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