Original Article

Randomized, double-blind study of minocycline vs. placebo in the treatment of progressive macular hypomelanosis

Estudo duplo-cego randomizado e comparativo entre minociclina e placebo no tratamento da hipomelanose macular progressiva

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ABSTRACT

Introduction: Progressive macular hypomelanosis is a common skin hypopigmentation found in all ethnicities, yet it is seldom diagnosed. It affects young adults, especially women, and is often mistaken with pityriasis alba and pityriasis versicolor. It is characterized by symmetric, well-defined, non-desquamative nummular hypopigmented macules in body areas with a greater concentration of sebaceous glands (trunk, thorax, abdomen and lumbar regions). Its etiology is poorly understood, and there is no effective treatment. A red fluorescence has recently been discovered in the lesion, suggesting the presence of porphyrin, produced by Propionibacterium acnes.

Objective: To compare the efficacy of 100 mg/day minocycline vs. placebo in the treatment of progressive macular hypomelanosis.

Methods: Patients over 18 (n = 20), who had suffered from the condition for more than 3 months (without treatment in the previous 3 months), who did not have an allergy to tetracycline, were randomized to receive minocycline or placebo. Wood's Lamp examinations and clinical evaluations (with descriptions and classifications using a color scale), and standardized picture records were conducted at baseline and 30 and 90 days after treatment.

Results: Eighteen patients completed the study. The group treated with minocycline presented a statistically significant improvement ($p < 0.05$) compared to the control group.

Conclusion: 100 mg/day minocycline for 30 days was effective in treating progressive macular hypomelanosis, meaning that Propionibacterium acnes probably has a role in the condition's pathogeny.

Keywords: minocycline; hypopigmentation; placebo effect; treatment.

RESUMO

Introdução: *A hipomelanose macular progressiva (HMP) é hipopigmentação comum da pele, porém pouco diagnosticada. Ocorre em todas as raças e tem sido encontrada no mundo todo. Atinge adultos jovens, especialmente mulheres, sendo muitas vezes confundida com pitiríase alba e pitiríase versicolor. Caracteriza-se por máculas hipopigmentadas numulares, não descamativas, bem definidas e simétricas, em áreas corporais de maior concentração de glândulas sebáceas (tronco, tórax, abdome e região lombar). Não há tratamento efetivo, e sua etiologia é pouco conhecida, mas recentemente foi descoberta fluorescência vermelha nas lesões, o que sugere a presença de porfirina, produzida pelo Propionibacterium acnes.*

Objetivo: *Avaliar a eficácia clínica do uso da minociclina 100mg/dia no tratamento da hipomelanose macular progressiva, comparado com grupo placebo.*

Métodos: *Foram incluídos 20 pacientes maiores de 18 anos, com tempo de doença superior a três meses, sem alergias a derivados de tetraciclinas, sem tratamento prévio pelo menos nos últimos três meses, e houve a randomização aleatória em dois grupos (10 pacientes no grupo placebo e 10 no grupo da minociclina). As seguintes avaliações foram realizadas (pré-tratamento, 30 e 90 dias após o término do tratamento): lâmpada de Wood, exame clínico com descrição das lesões além da classificação na escala de cor e fotografias padronizadas.*

Resultados: *Dos 20 pacientes incluídos, 18 completaram o estudo. Destes, o grupo que tomou minociclina teve melhora estatisticamente significante ($p < 0,05$) em comparação ao grupo-controle.*

Conclusão: *Minociclina 100mg/dia por 30 dias foi eficaz isoladamente no tratamento da HMP, relacionando o provável papel do Propionibacterium acnes na patogenia da doença.*

Palavras-chave: *minociclina; hipopigmentação; efeito placebo; tratamento.*

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INTRODUCTION

Progressive macular hypomelanosis is a common skin hypopigmentation that occurs in all ethnic groups and is found all over the world. It affects young adults, especially women, and is often mistaken with pityriasis alba and pityriasis versicolor.[1,2] Only one study has described an increase in incidence among men.[3]

Progressive macular hypomelanosis is characterized by well-defined and symmetrical hypopigmented nummular macules in body areas that have a greater concentration of sebaceous glands [2,4,5] (trunk, thorax, abdomen, lumbar region and proximal region of upper limbs); there is no systemic manifestation. Lesions are not preceded by inflammation, and get progressively worse. It occurs most commonly on the back (90%), followed by the abdomen (85%), buttocks (35%), thorax (15%) and upper extremities (5%).

Progressive macular hypomelanosis is an important dermatologic problem that stigmatizes the people that suffer from it, affects their daily activities, and elicits undesirable questions about the lesions.

Guilet and colleagues [6,7] found that the condition's progression phase lasts approximately one year, while its regression phase is most likely to last between two and five years. However, other authors believe that spontaneous regression does not occur and that hypomelanosis can remain stable for many years or progress slowly and gradually.[1,3]

Its etiology is still unknown. Dutch researchers 8 have observed follicular red fluorescence of the lesions under Wood's light, suggesting a possible correlation with the *Propionibacterium acnes* (*P acnes*) bacterium, which produces porphyrin. That type of fluorescence is not observed in patients with pityriasis alba or pityriasis versicolor. Westerhof and others [1] concluded that there must be a correlation between the presence of *P acnes* and the hypopigmented macules; they postulated that the bacterium produces the whitening factor that causes hypopigmentation.

Histopathologic findings are usually unspecific, however a common characteristic is a smaller amount of melanin in the lesion[9] and an absence of spongiosis. Using biopsies and electronic microscopy, Relyvelt and colleagues [4] compared the normal and affected skin of eight patients with a clinical diagnosis of progressive macular hypomelanosis and concluded that there was a decrease in melanin production and in the distribution of melanosomes. In other studies, Relyveld [4,5] and Westerhof 1 have found a high density of gram-positive bacteria compatible with *P acnes* through Gram staining

The proposed treatments described in the literature include phototherapy (Psoralen + ultraviolet A (PUVA), ultraviolet A (UVA) or narrowband ultraviolet B (NBUVB)), topical 5% benzoyl peroxide combined with 1% clindamycin, and oral minocycline. There is also a report of using oral doxycycline. One study compared benzoyl peroxide and clindamycin on one side of the body and fluticasone on the other, with UV exposure on both sides; the side treated with antimicrobials showed steady improvement.[5] In a case report, Perman and others [10] treated patients with doxycycline and UV radiation, and improvements lasted for six months. Duarte and colleagues [2] described improvement in both PUVA and NBUVB, however the lesions returned in 72% of their patients.

In a recent publication on approaches to acne treatment, the American Academy of Dermatology [11] asserted that "doxycycline and minocycline are more effective than tetracycline, with evidence that minocycline is superior to doxycycline in reducing the *Propionibacterium acnes* population."

A prospective, open, uncontrolled study demonstrated repigmentation in all patients after the use of 100 mg/day minocycline for three months, without the combined exposure to the sun. Eleven patients were followed up, and the clinical improvement was found to persist at least 11 months after the end of treatment.[12]

In the literature describing therapeutic success, it was not possible to find controlled, randomized double-blind studies. Most studies combine this treatment with exposure to UV radiation.

OBJECTIVE

To compare the clinical efficacy of 100 mg/day minocycline vs. placebo, without sun exposure, in the treatment of progressive macular hypomelanosis.

METHODS

This was a double-blind, randomized, placebo-controlled study of 20 progressive macular hypomelanosis patients of the Dermatology outpatient clinic of the Hospital Servidor Público Municipal de São Paulo, (SP) Brazil. Study participants were randomized to receive 100 mg/day minocycline or placebo for 30 days. All were instructed on the study's details and procedures and signed a term of informed consent and authorization for photographs to be taken. The study protocol was submitted to and approved by the Clinical Research Ethics Committee of the Hospital Servidor Público Municipal de São Paulo (n. 189/2010).

The diagnosis was based on the clinical appearance of the skin lesions, which were assessed by two dermatologist physicians who verified the presence of follicular red fluorescence under Wood's light and negative direct fungal examination.

The study included patients aged 18-60 years who had been inflicted with the disorder for more than three months and who had not taken topical, systemic, antibiotic or antifungal medication in the 3 months preceding the study. Pregnant or breastfeeding women, and patients with a hypersensitivity to tetracyclines, were excluded.

Twenty patients of both genders (17% men, 83% women) aged 18-60 (average 24 years), who had lesions for 8-240 months (average 54 months) on their back/abdomen (61%) or back (39%) were randomized.

The pre-treatment assessment involved a clinical examination that included a description of the lesions and standardized photographs, a direct fungal examination and assessment under Wood's light (long-wave UVA light beamed through Wood's fil-

ter, which only allows 320-400 nm wavelength radiation to pass through).[13,14]

In order to obtain a less subjective evaluation of clinical improvement, the hue of the normal and adjacent altered skin were compared using a numerical skin color scale (1 = lightest, 20 = darkest, see Figure 1). A decrease in the numerical difference between the affected skin of the macule and the normal skin (i.e., a lower contrast between the skin colors) signified clinical improvement. The photographs, taken with a Sony DSC-W170 digital camera, each used the same focal distance and lighting.

The patients were followed up 30 and 90 days after treatment. The clinical and Wood's light examinations, the classification with the numerical skin color scale, and photographs were repeated in the follow-up consultations, and possible adverse effects and intercurrences were assessed. Clinical improvement was defined as a decrease in the lesion's red fluorescence under Wood's light and an increase in the color scale score, with an emphasis on a decrease in the difference between the hues of the lesion and the normal skin. A smaller difference between the scores of the normal and affected skin indicated less color discrepancy, with the macule's color more closely matching that of the normal skin.

Fisher's and Student's t-tests were used in the statistical analysis to calculate relative risk. Statistical significance was defined as $p < 0.05$.

RESULTS

Of the 20 volunteers selected, 18 completed the study (nine in each group). Two participants dropped out due to travel and relocation. Between-group comparisons of gender, age, duration and lesion site, evaluations with Wood's light and difference in color between normal and affected skin before, 30 and 90 days after treatment is shown in table 1. There were no statistically significant differences in gender, age, site or duration of lesions between the placebo and medicated groups (Table 2).

Regarding clinical improvement, the statistical analysis indicated that there was a significant difference ($p = 0.0285$) and relative risk of 3.5. In the control group, 78% of patients did not improve, while 78% of patients in the medicated group presented clinical improvement, as shown in Table 2. Clinical improvement was quantified according to the numerical skin color scale's gradient (0: absence of improvement in the macule's color; 1: darkening of the macule's color by one hue; 2: darkening of the macule's color by two hues, and 3: darkening of the macule's color by three hues). As shown in Table 3, 22% of patients in the medicated group did not demonstrate clinical improvement; 34% presented a one-point improvement in the color scale, 22% improved by two points, and 22% improved by three points, with a more significant and evident improvement in the last group (Figure 2). In the placebo group, only 22% of patients demonstrated a two-point improvement.

All nine patients (100%) of the placebo group continued to demonstrate red fluorescence under Wood light. Six patients (67%) in the medicated group stopped displaying red fluorescence after treatment, and three (33%) remained unchanged.

None of the patients in the placebo group presented any side effects, while five medicated patients (56%) presented mild side effects (nausea, vomiting, improvement of acne), and four (44%) did not present any symptoms linked to the use of minocycline.

DISCUSSION

The term progressive macular hypomelanosis was used for the first time by Guillet and colleagues to describe lesions in young women in Southern India and in the population of Caribbean immigrants in France.6 Other descriptions of this condition are "*Cutis trunci Variata*,"[15] "*Creole dyschromia*," [7] "*Idiopathic multiple large-blemish hypomelanosis* "[16] and "*Extensive pityriasis alba*."[17]

While its prevalence is unknown, it is believed to be very common, but is seldom diagnosed because it is often confused with other pathologies that present a similar clinical picture. For that reason, direct fungal examination was carried out in the lesions, and a negative result was found in all study patients.

In this study, lesions were located on the abdomen and back, with an average duration of 54 months, and there was predominance in women (83% of cases) and a higher incidence among young adults, all of which coincides with the data described in the literature. Although this pathology's predominance in women has been described in many studies, this finding might be partly explained by the fact that women seek dermatological care more frequently. Although it has been described as rarely affecting patients older than 30,1 three study patients fell into that age group (36, 43 and 46 years old).

Progressive macular hypomelanosis' etiology is uncertain. Among the explanations of its origins are genodermatoses 1,8 and, more recently, a correlation with *P acnes*. The link with *P acnes* is based on the observation of follicular red fluorescence under Wood's light and a positive culture of *P acnes* in the lesions, as demonstrated by Westerhoff and others. 1 In a recently published case report, Neynaber and colleagues found no evi-

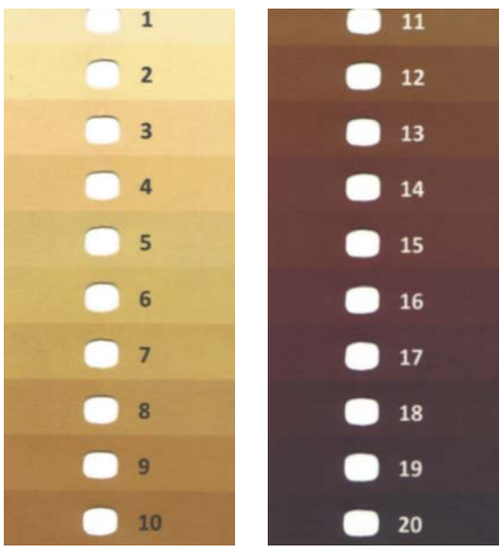


Figure 1 – Skin color level classification scale

Table 1- Study population features

Patient's number	Gender	Age	Lesion site	Duration (months)	Wood light before treatment	Wood light 30 days after treatment	Wood light 90 days after treatment	Skin color level before treatment	Skin color level 30 days after treatment	Skin color level 90 days after treatment	Clinical improvement	Medication
6	Female	18	Abdomen/back	12	+	+	+	7	7	7	No	Minocycline
18	Female	18	Abdomen/back	8	+	+	+	4	4	4	No	Minocycline
2	Female	43	Abdomen/back	240	+	+	-	7	7	6	Yes	Minocycline
5	Female	18	Abdomen/back	24	+	+	-	7	7	6	Yes	Minocycline
7	Female	18	Back	48	+	+	+	6	5	5	Yes	Minocycline
9	Female	21	Abdomen/back	24	+	+	-	5	5	2	Yes	Minocycline
10	Female	18	Back	36	+	-	-	5	4	3	Yes	Minocycline
14	Female	18	Abdomen/back	36	+	-	-	4	2	1	Yes	Minocycline
15	Female	18	Back	36	+	-	-	7	6	5	Yes	Minocycline
1	Female	30	Abdomen/back	96	+	+	+	6	6	6	No	Placebo
8	Female	21	Back	96	+	+	+	7	7	7	No	PlaceboFemale x
11	Female	26	Back	24	+	+	+	9	9	9	No	Placebo
12	Female	18	Back	48	+	+	+	15	15	15	No	Placebo
16	Female	18	Abdomen/back	24	+	+	+	11	11	11	No	Placebo
4	Male	36	Abdomen/back	48	+	+	+	5	5	5	No	Placebo
13	Male	20	Abdomen/back	48	+	+	+	7	7	7	No	Placebo
3	Female	19	Back	12	+	+	+	11	10	9	Yes	Placebo
17	Male	46	Abdomen/back	120	+	+	+	8	7	6	Yes	Placebo

Note: The figures in the skin color level columns before, 30 days after and 90 days after treatment refer to the difference between the color levels of the affected and normal skin. A decrease in that difference corresponds to a clinical improvement, meaning a less intense contrast between the colors of the affected and normal skin

dence of *P acnes* using Wood's light or in the histopathologic analysis, which used a special stain for bacteria.[18]

In the present study, all patients who were clinically diagnosed before treatment presented positive red fluorescence under Wood's light, a result that was sustained after treatment in all patients in the placebo group (Table 4).

There is no consensus on a widely recognized and effective treatment option. Kwah and others [19] evaluated the effectiveness of NBUVB as a monotherapy, which demonstrated satisfactory yet short-lived results. Duarte and colleagues [2] found similar satisfactory results with PUVA and NBUVB; there was no statistically significant difference between the two methods. However, 72% of the patients experienced a recurrence of the lesions.

Based on Westerhoff and others' hypothesis [1] about the inhibitory role of *P acnes* in melanogenesis, some authors have used antibiotics to treat progressive macular hypomelanosis. One study obtained satisfactory results with the topical combination of 5% benzoyl peroxide gel and 1% clindamycin, [5] while another also obtained a satisfactory outcome in one case using topical benzoyl peroxide and erythromycin [20]. A third case successfully used a combination of doxycycline and sun exposure. [10] An earlier pilot study (prospective, open, non-controlled) conducted by the authors found that 100 mg/day minocycline for three months stimulated repigmentation in all patients even without exposure to the sun. No recurrences were observed in the 11 months of post-treatment follow-up.[12]

In therapeutic successes reported in the literature, no other randomized, placebo-controlled, double-blind studies that did not involve solar exposure were found. The present research yielded improvement in seven out of nine individuals who used the medication, which matches the satisfactory results of minocycline described by Almeida and colleagues [12]. Yet repigmentation occurred in only two cases in the placebo group.

Despite descriptions of rare cases of hypersensitivity to minocycline,[21] induction of lupus-like, autoimmune hepatitis, hyperpigmentation and vasculitis, [22,23] the only effects reported in this study were nausea and vomiting in three patients and improvement of acne in two (56% of patients in the medicated group). Although the causes of these effects are not fully understood, hypotheses have been proposed that suggest a reduction in the production of free radicals, inhibition of phospholipase a^2, and changes in the expression of the tumorous necrosis factor and alpha interferon are involved.[24-26] The improvement in acne can be even considered as an advantage provided by the medication that increases patient satisfaction.

Of the nine participants in the minocycline group, two (22%) did not respond. This outcome might be explained by the duration of the treatment (30 days), which is considerably less than the three months described by Almeida and col-

Table 2 - Comparison of variables between placebo and minocycline groups (gender, lesion site and duration, age, clinical improvement and side effects)

Characteristics		Drug				Total (n=18)		Relative risk	p- value	Test
		Minocycline (n=9)		Placebo (n=9)						
		Number of patients	%	Number of patients	%	Number of patients	%			
Gender	Male	0	0%	3	33%	3	17%	–	0,2059	Fisher's exact
	Female	9	100%	6	67%	15	83%			
Lesion site	Abdome/ Back	6	67%	5	56%	11	61%	1,27	1000	Fisher's exact
	Back	3	33%	4	44%	7	39%			
Clinical improvement	Yes	7	78%	2	22%	9	50%	3,5	0.0283	Fisher's exact
								sig		
	No	2	22%	7	78%	9	50%			
Age (years)	Average	21		26		24		–	0,2670	Student-t
	CI 95%	14,76 to 27,47		18,54 to 33,46		19,03 to 28,08				
Duration (months)	Average	52		57		54		–	0,8336	Student-t
	CI 95%	-3,63 to 106,74		28,25 to 86,427822		26,72 to 82,17				
Side effects	No	4	44%	9	100%	13	72%	–	0.0147	Fisher's exact
	Yes	5	56%	0	0%	5	28%		sig	

Table 3: Medicated group's clinical improvement quantification using the skin color level scale

Result	Minocycline (n = 9)		Placebo (n = 9)	
	Number of patients	%	Number of patients	%
0	2	22	7	78
1	3	33	0	0
2	2	22	2	22
3	2	22	0	0
Total	**9**	**100**	**9**	**100**

Table 4: Medicated group's Wood light fluorescence evaluation before and 90 days after treatment

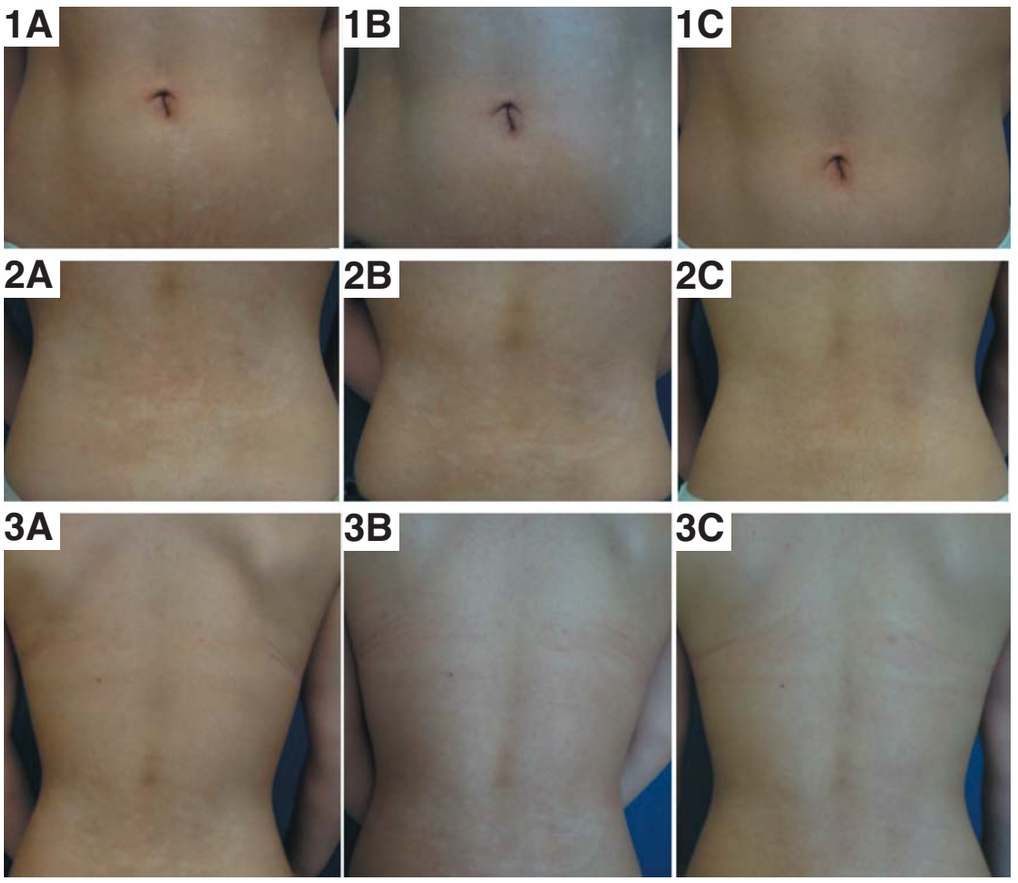
Fluorescence under Wood light	Pre-treatment		90 days after treatment	
	Number of patients	%	Number of patients	%
+ 9	100	3	33	
–	0	0	6	67
Total	**9**	**100**	**9**	**100**

leagues' study [12] that demonstrated 100% repigmentation in all treated cases.

The statistically significant difference between the cases treated with placebo and minocycline demonstrates that the latter – a recognizably effective agent against *P acnes* even when not combined with UV exposure – is an effective therapeutic option in treating progressive macular hypomelanosis. Studies with a larger sample and a longer follow-up period are necessary to confirm these results and assess their long-term permanence.

CONCLUSION

The use of 100 mg/day minocycline for 30 days was effective in treating progressive macular hypomelanosis, even without solar exposure. ●



Figures 2: Clinical improvement in the minocycline group:
1A, 2A and 3A: Before treatment;
1B, 2B and 3B: 30 days after treatment;
1C, 2C and 3C: 90 days after treatment

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