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Is Benzoyl Peroxide and Clindamycin Effective Combination Treatment for Progressive Macular Hypomelanosis in Adults?

Samantha Colosi
Philadelphia College of Osteopathic Medicine, Samanthacol@pcom.edu

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Samantha Colosi, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not there is efficacy with combination treatment benzoyl peroxide and clindamycin for progressive macular hypomelanosis in adults.

Study Design: A review of three English language studies. One published in 2006 and two in 2011. Includes two RCT's and one randomized left-right comparison study.

Data Sources: Researched articles via PubMed and Cochrane database. All articles were published in peer-reviewed journals. Two randomized, controlled trials and one randomized left-right comparison study were used.

Outcomes Measured: The outcomes measured by: subjective patient ratings based on photographs before and after treatment and two dermatologists' ratings. Relyveld et al study and Sim et al study in addition used a color analyzer.

Results: The two randomized, controlled trials and the left-right comparison study showed that the use of clindamycin and benzoyl peroxide was effective in the treatment of progressive macular hypomelonosis in adults. Results from these three studies showed Improvement of the overall PMH lesions by the investigator, patient, dermatologist and color analyzer (quantitatively compares discoloration, erythema, pigmentation and skin color).

Conclusions: The results of the randomized, controlled trials and left-right comparison study indicate that combination products clindamycin and benzoyl peroxide are effective in the treatment of progressive macular hypomelonosis. All three studies also demonstrated that benzoyl peroxide and clindamycin were safe when used to treat PMH.
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Key Words: progressive macular hypomelanosis; clindamycin, benzoyl peroxide

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.[3] The lesions are not preceded by inflammatory disease and tend to increase progressively in number. Histopathologically, the skin lesions show a decrease in melanin content in the epidermis compared with the adjacent skin without lesions. No other abnormalities are seen in the epidermis or dermis such as spongiosis or other signs of eczematous inflammation.[4] There is no consensus or first-line therapy in the treatment of PMH and the treatment options used are very little effective.[3]

PMH has been reported in patients with skin type's I-III.[2] It occurs in all races and has a worldwide distribution, but it is more frequently identified in young adults/women and African American people from tropical countries, but the prevalence studies are scarce.[3] In 1994, Lesueur et al diagnosed 121 cases of PMH during a screening for leprosy among 511 patients in the French West Indies (Martinique). Also in Martinique, Guillet et al diagnosed 150 new cases in their dermatology clinic.[2] PMH can cause cosmetic problems for patients, which can lead to a negative impact on the patient's quality of life. Since, this condition is frequently misdiagnosed; no exact percentage is given to determine how much money is spent annually.[1] However, due to the numerous individuals affected by progressive macular hypomelanosis, this condition is commonly encountered in the scope of PA practice. Therefore, it is important to be able to correctly diagnose and treat PMH.

The diagnosis is clinical and the main differential diagnosis is pityriasis versicolor.[3] To differentiate pityriasis versicolor from PMH potassium hydroxide test results of epidermal

scrapings are performed.[2] The clinical findings of PMH include the presence of red follicular fluorescence in the hypopigmented spots when illuminated with a wood's lamp in a dark room.[2]

Unfortunately, little is known about the origin and pathogenesis of PMH. [2] One thought is the presence of propionibacterium acnes (P. acnes) in the hypopigmented macules playing an important role in the development of PMH. Similar to the Malassezia species in tines versicolor, it is possible that P. acnes produces a depigmenting factor that disrupts melanogenesis and induces hypopigmented lesions. Since a bacteria may contribute to the cause of PMH it makes sense that antimicrobial therapy would be used for the treatment of PMH and has been associated with clinical improvement.[4]

Numerous therapy options have been used with variable results for the treatment of PMH, including local hydration, sun exposure with UVA/UVB, phototherapy, topical corticosteroids and oral tetracycline. 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. However, the combination of benzoyl peroxide 5% and clindamycin 1% has shown to be quite effective against P. acnes as previously mentioned. The combined use of both of these products reduces the risk of development of resistant P. acnes. Elimination of P. acnes with a topical antimicrobial therapy could therefore improve repigmentation in patients with PMH.[3]

Objective

"The objective of this selective EBM review is to determine whether or not there is efficacy with combination treatment benzoyl peroxide and clindamycin for progressive macular hypomelanosis in adults."

Methods

The population in these studies consisted of healthy men and women over the age of twenty-one with a diagnosis of PMH. The interventions used were 5% benzoyl peroxide and 1% clindamycin. The treatment groups receiving benzoyl peroxide and clindamycin were compared to those receiving either UVA/fluticasone 0.05%, gel placebo, or narrow band ultraviolet B (NBUVB). The outcomes measured were those of patient-oriented evidence. There was improvement of the overall PMH lesions by the investigator, patient, dermatologist and color analyzer (quantitatively compares erythema, pigmentation and skin color). This review includes two randomized control trials and one randomized left-right comparison study.

The three studies in this review were researched using PubMed and Cochrane database by the author. Keywords used in literature search were "progressive macular hypomelanosis", "clindamycin", and "benzoyl peroxide". All articles were published in English in peer-reviewed journals. One article was published in 2006 and the other two articles in 2011. Articles were selected by the author based on their relevance and outcome to the patient. All three reviews had similar inclusion and exclusion criteria. The Inclusion criteria were healthy men and women over 21 years old with a diagnosis of PMH. The exclusion criteria were pregnant or lactating females, allergies to products given or history of pityriasis versicolor. **Table 1** demonstrates the demographics of the studies included. Statistics included in the studies were relative benefit increase (RBI), absolute benefit increase (ABI), relative risk increase (RRI), absolute risk increase (ARI), number needed to treat (NNT), number needed to harm (NNH), and p-values.

Table 1: Table of demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Relyveld 2006 (2)	RCT	45	16-55	Ages 16-55 with	Positive potassium	7	Benzoyl peroxide 5%

				diagnosis of PMH	hydroxide test results; sensitive to any of the study medication ingredients, pregnant or lactating		hydrogel & clindamycin 1% lotion & UVA VS. Fluticasone & UVA
Santos, 2011 (3)	RCT (double blind placebo controlled)	23	>15	>15, clinical diagnosis of PMH confirmed by two dermatologists, negative mycological examination & no previous treatment for 30 days	Pregnant or lactating females, patients with associated disease & patients allergic to the therapy drugs used in this study or sensitive to sunlight	0	Benzoyl peroxide 5% & Clindamycin 1% VS. Visually matched placebo
Sim, 2011 (4)	Randomized left-right comparison study	10	21-43	Ages 21-43, with a diagnosis of PMH	History of pityriasis versicolor or other inflammatory disorders in the hypopigmented spot, sensitive to any ingredients of the study medications or sunlight, treated with other treatments, pregnant or lactating females	3	NBUVB with benzoyl peroxide & clindamycin VS. NBUVB monotherapy

Outcomes Measured

Outcomes measured were those of patient-oriented evidence that matters. All three articles measured the efficacy of repigmentation/decrease incidence of hypopigmentation of

PMH by subjective patient ratings (based on photographs taken before and after treatment) and by two dermatologists. The differences between these studies are the Relyveld et al study also measured the skin with a color analyzer at baseline; after 2, 6, 10, and 14 weeks of treatment; and after a period of 12 weeks without treatment (26 weeks). This color analyzer transforms a reflectance spectrum R (λ) into 3 values: L^*, a^*, and b^*. L^* represents the lightness of the spectrum and varies from 0 for a black object to 100 for a white object, a^* represents green (negative values) and red (positive values), and b^* represents blue (negative values) and yellow (positive values).[2] Santos et al measured efficacy on photographs, but they were taken on day's 0, 15, 60 and 90. 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.[3] Lastly, Sim et al study in addition to using the photographs, also used the color analyzer. This study rated the efficacy of repigmentation on a score from 0-4; 0-5%, no change; 1, 6-25% repigmentation; 2, 26-50% repigmentation; 3, 51-75% repigmentation; 4, 76-100% repigmentation.[4]

Another outcome measured was adverse events of benzoyl peroxide and clindamycin. This was evaluated by the side effects and physical examination findings. Though there were some effects documented, this never deterred patients from using the medication or caused them to not follow-up.

Results

This EBM review was done on two randomized controlled trials and one randomized left-right comparison study. The results of the two randomized controlled trials were presented as dichotomous data; therefore, I will display the results of those two studies together in **Tables 2 & 3** and the left-right comparison study separate. Data from the two dichotomous studies were

analyzed with the intention to treat.

In the Relyveld et al study, after fourteen weeks of treatment, both the treated sides became darker than normal skin, but this effect was more pronounced on the bcUVA (benzoyl peroxide/clindamycin + UVA) side. After twelve weeks without treatment, the antibacterial (bcUVA)-treated side had the same degree of pigmentation as normal skin whereas the anti-inflammatory fUVA (fluticasone + UVA)-treated side was lighter than normal skin. Although the skin on the bcUVA side remained evenly pigmented, hypopigmentation macules reappeared on the fUVA side. The patients and dermatologists scored the bcUVA-treated side higher than the fUVA-treated side. This difference was highly significant after fourteen weeks of treatment ($P < .0001$ for patients, $P < .0001$ for dermatologists). At the end of the follow-up, 62% of the patients judged their bcUVA-treated side as totally repigmented, but only 13% of the patients gave such a score to their fUVA-treated side ($P < .0001$). The dermatologists scored 62% of the bcUVA-treated sides and 22% of fUVA-treated sides as totally repigmented at the end of the follow-up ($P < .0001$). Most adverse effects were mild and followed anticipated patterns. More patients reported cutaneous side effects with antibacterial than with corticosteroid therapy (71% vs. 24%, $P < .0001$). The incidence of side effects decreased after the second week of both treatments. After the sixth week, only four (9%) patients mentioned side effects on the bcUVA side and three (7%) patients mentioned side effects on the fUVA side.[2] Unfortunately, the study did not list what the exact side effects were, therefore, it is not documented in this paper.

In the Santos et al study 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 placebo. Patients were advised to expose themselves to the sun on daily basis and were systematically evaluated and photographed. The collected data was entered and analyzed. A p

value < 0.05 was considered statistically significant. 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. Seven patients, (53%) in group A, showed complete recovery of lesions 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.[3] **Table 2** shows the efficacy of benzoyl peroxide 5% and clindamycin 1% in the treatment of progressive macular hypomelanosis in the two studies just discussed. **Table 3** shows the incidence of side effects in patients treated with benzoyl peroxide and clindamycin versus the control fUVA for Relyveld et al study or placebo for Santos et al study.

Table 2 Clinical efficacy of benzoyl peroxide and clindamycin in the treatment of PMH

Study	CER (fUVA) for Relyveld, (placebo) for Santos	EER benzoyl peroxide 5% + clindamycin 1%	p-value	RBI	ABI	NNT
Relyveld, 2006	22%	62%	P < .0001	180%	40%	3
Santos, 2011	20%	85%	P < 0.003	330%	65%	2

CER – control event rate, EER – experimental event rate, RBI – relative benefit increase, ABI – absolute benefit increase, NNT – number needed to treat

Table 3 Incidence of side effects in patients treated with benzoyl peroxide & clindamycin vs. control

Study	CER (fUVA) for Relyveld, (placebo) for	EER benzoyl peroxide 5% +	RRI	ARI	NNH

	Santos	clindamycin 1%			
Relyveld, 2006	24%	71%	200%	47%	3
Santos, 2011	15%	85%	470%	70%	2

EER – experimental event rate, CER – control event rate, RRI – relative risk increase, ARI – absolute risk increase, NNH – number needed to harm

Lastly, I will discuss the Sim et al study which since it was not presented in dichotomous data; I will discuss the results narratively. After 8 weeks of treatment, significant repigmentation appeared at both of the treated sides compared with the initial evaluation. The mean difference in L values between the skin lesions and adjacent skin without lesions was 4.52 ± 1.65 at the initial evaluation and was reduced significantly to 0.94 ± 0.65 during the treatment period in the comb-NBUVB area (benzoyl peroxide & clindamycin + UVB), and in the mono-NBUVB (UVB) area, it was 4.34 ± 1.39 and 1.18 ± 0.94 respectively ($P < 0.05$). However, there were no significant differences between each treated site at both of the evaluation points in time. At 6 months after treatment, clinical improvement remained in four of seven patients; however, almost recurrence occurred in the other patients. The mean difference in L values between the skin lesions and adjacent skin without lesions was 1.86 ± 1.42 in the comb-NBUVB area and 2.05 ± 1.55 in the mono-NBUVB area, and this difference was not statistically significant. There were minimal side effects in this study. Five patients complained of transient irritation and two patients complained of erythematous skin eruption in the comb-NBUVB area and this resolved following daily application of anti-microbial gel. All adverse effects were mild and resolved with topical corticosteroid therapy.[4]

Discussion

In the Relyveld et al study, antibacterial therapy with UVA was more effective than anti-inflammatory therapy with UVA in the treatment of PMH. Anti-bacterial therapy led to better

repigmentation as indicated by darker objective skin measurements and, more importantly, by higher score for treatment success by both patients and dermatologists.[2] One limitation to this study or a recommendation I would suggest for the future would be a more thorough investigation on the medicines used. This study did not explore the optimal dose for benzoyl peroxide and clindamycin, other routes of administration, or whether other types of antibiotics are equally effective.

In the Santos et al study, the use of topical combination of benzoyl peroxide 5% and clindamycin 1% showed improvement in PMH. 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. The choice of the antimicrobial was due to the fact that combination of benzoyl peroxide 5% and clindamycin 1% are very effective against P. acne, easy to apply and has few systemic side effects. The main limitations of this study were small sample size 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.[3]

In the Sim et al study the comb-NBUVB treatment was not superior to mono-NBUVB treatment in patients with PMH. Even though both treatments showed improvement in repigmentation after eight weeks, there was no significant difference to determine which treatment was more effective. At the six month follow-up recurrence occurred in some participants. Even though recurrence occurred in some patients, NBUVB combined with benzoyl peroxide and clindamycin appears to be a safe and useful modality for the treatment of PMH. One limitation was the study did not have enough statistical power to support the equivalent

clinical results between the treated sites at both evaluation points in time because of the small number of enrolled patients. Therefore, further investigation with a larger number would be needed for relevant results.[4]

Conclusion

The trials reviewed imply that benzoyl peroxide 5% and clindamycin 1% is safe and effective for the treatment of progressive macular hypomelanosis. Patients in all three studies showed improvement in their PMH when applying topical benzoyl peroxide and clindamycin. It was also suggested from these studies that benzoyl peroxide and clindamycin are well-tolerated, as it does not cause significant adverse events. Benzoyl peroxide and clindamycin combination treatment provides a new treatment option for medical providers and those diagnosed with PMH. Although these studies do conclude the use of benzoyl peroxide and clindamycin are safe and effective, more trials should be done to assess the safety of using these two treatment options over a chronic time period, such as: exploring the optimal dose for benzoyl peroxide and clindamycin, other routes of administration or whether other types of antibiotics are equally effective. Regardless of the need for additional studies, benzoyl peroxide and clindamycin is a safe and effective way of treating progressive macular hypomelanosis.

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