# AN ACNE STUDY FOCUSED ON ERYTHROMYCIN: BENZOYL PEROXIDE ALONE OR WITH TOPICAL ERYTHROMYCIN AGAINST PROPIONIBACTERIUM ACNES IN ACNE VULGARIS

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*ABSTRACT*

***Purpose:*** *Acne vulgaris is a common disease of the pilosebaceous unit. Antibiotics and non-antibiotic antimicrobial drugs which reduce the growth of Propionibacterium acnes (P. acnes) are of therapeutic value. The study aimed to compare the activity of benzoyl peroxide 5% with or without topical erythromycin 3% against P. acnes and to determine the development of antimicrobial resistance.* ***Methods:*** *A double-blind, randomized study was performed on 75 patients with mild to moderate acne vulgaris. The effect of treatment was assessed by lesion counting system. Samples were obtained from the forehead at 0, 4, 8, 12 and 16 weeks of treatment. Brain heart infusion agar with supplements was used for isolation of P. acnes in an anaerobic chamber. Agar dilution method was perfomed for minimal inhibitory concentration (MIC) of erythromycin.* ***Results:*** *Both treatment groups produced significant clinical improvements with no better results in the combination therapy group. Reduction in the total lesion counts was similar in both groups at the end of treatment. The* $MIC_{90}$ *value of P. acnes was 0.125 μg/ml for erythromycin prior to therapy. Isolation rate of P. acnes was similar in both treatment groups. MIC values of erythromycin were higher in P. acnes isolated from the combination therapy group than benzoyl peroxide group (*$p<0.001$*).* ***Conclusion:*** *These data suggest that the combination of erythromycin and benzoyl peroxide is not synergestic against P. acnes and resistance to erythromycin develops with the combination therapy.*

***Key Words:*** *Acne, Benzoyl Peroxide, Propionibacterium Acnes, Erythromycin, Resistance.*

## INTRODUCTION

Acne vulgaris is a common disease of the pilosebaceous unit, that affects both males and females between the ages of 11 and 30 years (1). The disease is localised to skin regions such as the face, back and chest, where numerous pilosebaceous units are located. The development of acne depends on increased sebum production, ductal cornification, bacterial colonization of the pilosebaceous duct and inflammation (2,3). Propionibacterium acnes (P. acnes) is among the resident cutaneous microflora of the skin. It is one of the main factors which take part in cutaneous inflammation. Antibiotics and non-antibiotic antimicrobial drugs which reduce the growth of P. acnes have therapeutic value (2). Benzoyl peroxide has a strong antimicrobial effect and is used widely in our region. This study

is aimed to compare the activity of benzoyl peroxide with or without erythromycin against P. acnes to determine the development of antimicrobial resistance.

## MATERIALS AND METHODS

A double-blind, randomized study was performed on 75 patients with mild to moderate acne vulgaris. Patients received no oral or topical anti-acne therapy for four weeks prior to the study.

Thirty-eight patients were treated with twice daily applications of 5% benzoyl peroxide (Aksil-5® cream) and 37 patients with 5% benzoyl peroxide with 3% erythromycin (Benzamycin® gel). The effect of treatment was assessed by the lesion counting system. Samples were obtained from the forehead at 0, 4, 8, 12 and 16 weeks of treatment by using the detergent scrub technique (4). Medication was not applied on sampling days.

Sampling solution was composed of 0.075 M phosphate buffer containing 0.1% Tween 80 (5). The sample was transported immediately and cultured in brain heart infusion (BHI) agar. The culture media contained 3% (w/v) additional glucose (BHIg) and 2 μg/ml furazolidone (Sigma Chemical Co, Poole, Dorset, UK) to inhibit the growth of staphylococci. Incubation was carried out for 7 days at 37°C in anaerobic conditions. P. acnes was identified by conventional methods (6,7). API 20A (Bio-Meriéux, Marcy l'Etole, France) test strips were used for unidentified propionibacteria-like colonies. Minimum inhibitory concentrations (MIC) of erythromycin were determined by agar dilution methods in the range of 0.007 to 1024 μg/ml on BHI agar containing 0.75 g/lt additional glucose.

The patients with resistant P. acnes strains were excluded from the study at the beginning of the treatment.

The difference in lesion counts (Fig. 1) and MIC values (Fig. 2) between the two groups for each week of treatment were analyzed by Mann-Whitney U test. This study was carried under Good Clinical Practice standards.

## RESULTS

Data were obtained from 75 patients (23 males, 52 females) with a mean age of 18,4 ± 3,2

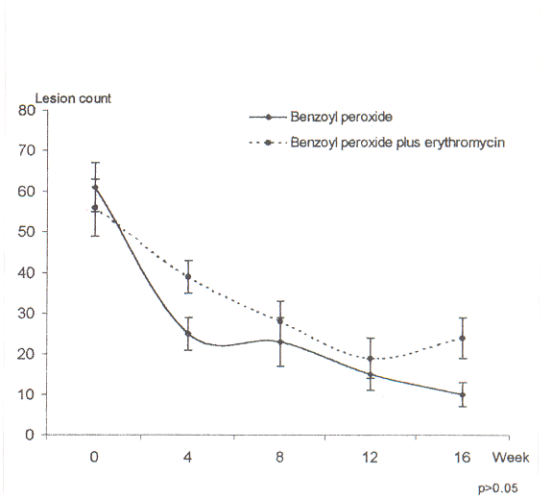


Fig. 1 : Lesion counts in treatment groups for each treatment week.

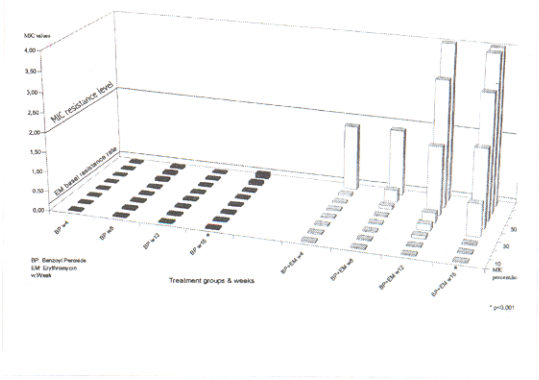


Fig. 2 : Comparison of the MIC values of the isolated Propionibacterium acnes strains for benzoyl peroxide and combination therapy groups for each week of treatment.

(range: 11 to 25) years. Thirty eight patients (8 male, 30 female, mean age 18.0 ± 3.7 years, (range: 14 to 25 years) were treated with 5% benzoyl peroxide and 37 patients (15 male, 22 female, mean age 18.9 ± 2.7 years, (range: 14 to 25 years) with the combination therapy.

Figure 1 shows the total lesion counts of the patients during the treatment period. Reduction in the total lesion counts was similar in both groups at the end of treatment.

The $MIC_{90}$ value of P. acnes was 0.125 μg/ml

for erythromycin prior to therapy. The isolation rate of P. acnes did not differ in the two groups for each week of treatment. Figure 2 shows the comparison of MIC percentiles of isolated P. acnes for both treatment groups. The MIC values of erythromycin were higher in the combination therapy group than the benzoyl peroxide group ($p<0.001$).

**DISCUSSION**

As a therapeutic drug benzoyl peroxide alone and combinted with erythromycin are commonly used in acne vulgaris in certain European countries and in the rest of the world. Several studies have indicated that the use of erythromycin in combination with benzoyl peroxide is more effective than the use of either agent alone. However, resistance to macrolide-lincosamide-streptogramin group (MLS) antibiotics may restrict the use of combination preparations (8-10). Long term surveillance programs show that antibiotic resistance should be screened during and after antimicrobial treatment modalities (8, 11).

In this study, as the treatment progressed, a marked resistance developed in the combination therapy group (Fig. 2) and the initial good therapeutic response decreased gradually. The difference between the two curves showing the total lesion counts for each treatment group was not statistically significant ($p>0.05$). The therapeutic response was better in the benzoyl peroxide group at four weeks of therapy (Fig. 1). The difference between the formulations of benzoyl peroxide might have a role in the therapeutic response. Another trial is needed to compare the efficacy of gel and cream formulations of benzoyl peroxide.

In our region, erythromycin resistance of P. acnes was detected as 7.1% for the teenage population with acne vulgaris (12). Topical erythromycin has recently been introduced for use, and oral erythromycin is not preferred as the firstline drug of choice for acne. Therefore the incidence of erythromycin resistance is expected to be low.

Patients with erythromycin resistant propionibacteria in skin scrub samples were excluded at the beginning of treatment. The MIC values of isolated P. acnes strains in benzoyl peroxide and the combination therapy groups were different for each week of treatment. In benzoyl peroxide therapy group the MIC values and MIC percentiles remained the same through the treatment weeks. In the combination therapy group, the MIC values and percentiles gradually increased, and reached higher values at the end of treatment (Fig. 2). These high MIC values correlate with the worsening therapeutic response. Resistant P. acnes strains might have activated different factors which prolonged the duration of inflammation and led to a worsening therapeutic response. Resistance depends on the choice of therapeutics and resistant bacteria may limit the therapeutic value of combination preparations. In Eady's report antibiotic policies are discussed for acne. Nevertheless, it is reported that there is no increase in the incidence of serious antibiotic-resistant systemic infections with P. acnes, in the long term antibiotic therapy for acne (13).

The MLS antibiotics are preferred in combination preparations. However, Eady et al. report that P. acnes may not be eradicated with MLS antibiotics, and cross resistance may develop with the local use of these antibiotics (8). Furthermore, close personal contact may ease the spread of these resistant strains, and the resistant genes may be transferred to the skin flora. The resistance may reduce the antibiotics' value for treating other infections. It is reported that antibiotics with important systemic indications should not be applied topically. The potential risk for the development of antibiotic resistance led some clinicians to prefer equally effective topical agents for treating acne, and to restrict the use of topical antibiotics to patients who did not respond to other medications. (14,15).

Benzoyl peroxide alone or with erythromycin is an effective treatment for acne vulgaris. However, these data suggest that the combination of erythromycin and benzoyl peroxide is not synergestic against P. acnes and resistance to erythromycin develops with the combination therapy. Local resistance data should be considered while evaluating an acne patient and today's treatment approach should let future patients benefit from antibiotic treatment (14,16).

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