

Topical 5% Benzoyl Peroxide and 3% Erythromycin Gel: Experience with 191 Patients with Papulopustular Acne

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Received: April 5, 2012

Accepted: January 10, 2013

SUMMARY Acne is the most common skin disease, with a relative prevalence of 85%-100% among young individuals. It affects the cosmetic appearance of the patients provoking severe distress. A number of different topical treatments have been used for the treatment of acne. In this study, we investigated the efficacy and safety of the topical treatment with 5% benzoyl peroxide and 3% erythromycin gel in patients with papulopustular acne. One hundred and ninety-one patients with inflammatory acne completed the study. The patients included 54 males and 137 females, mean age 22.3±8.1 years. Topical gel was applied on the face once daily for 3 months. The mean number of non-inflammatory and inflammatory lesions after 3 months of therapy decreased significantly with respect to baseline, with a mean percentage reduction of the non-inflammatory and inflammatory lesions by 42.2% and 57.5%, respectively. In conclusion, topical 5% benzoyl peroxide and erythromycin 3% as monotherapy is efficient for the treatment of papulopustular acne.

KEY WORDS: papulopustular acne, treatment, topical treatment, 5% benzoyl peroxide gel, erythromycin 3% gel, antibiotics

INTRODUCTION

Acne is the most common skin disease with a relative prevalence of 85%-100% among young individuals (1). It is considered a disorder of the pilosebaceous follicle with most common features being an increased sebum production, follicular keratinization, localized inflammation and colonization by *Propionibacterium acnes* and *Staphylococcus epidermidis* (2,3).

There are various types of acne, depending on the severity of the condition and acne vulgaris is considered the most frequent one. It affects the cosmetic appearance of the patients, provoking severe distress. Several different topical therapies have been used for

the treatment of acne. Although safe, a dramatic increase in bacterial resistance over the past 20 years has been seen, probably as a result of the use of topical antibiotics (4,5), leading to combination products of different topical treatments.

The combination of 5% benzoyl peroxide-erythromycin 3% (gel Erybenz[®], Verisfield, Athens, Greece) has been approved and introduced in the Hellenic market since March 2008. The present study aimed to provide additional evidence for the efficacy of 5% benzoyl peroxide-erythromycin 3% gel used as monotherapy for the treatment of papulopustular acne.

MATERIALS AND METHODS

Patient selection

The study was conducted from October 2009 to April 2010 in Athens and Tripolis, Greece. The individuals included in this study were 55 outpatients that were examined in the Dermatological Department of the Veterans Administration Hospital, 27 outpatients examined in the Dermatological Department of the Attikon General University Hospital and 123 patients examined in private practices. The study protocol was approved by the Ethics Committee of the participating hospitals and the patients signed informed consent forms.

The eligibility criteria were mild to moderate papulopustular acne (grade II-III by the Pillsbury classification system) (6), with inflammatory lesions (>10 pustules and/or papules) and non-inflammatory features (>10 comedones) on the facial area.

The criteria for patient exclusion were as follows: (a) pregnant and breast feeding women; (b) children under the age of 11 years; (c) severe cases of acne (presence of nodules and cysts); (d) patients on systemic treatment with isotretinoin, hormones or antibiotics for acne or other condition; (e) patients receiving topical anti-acne treatments (benzoyl peroxide, retinoids, azelaic acid) or topical corticosteroids for the last month; (f) patients taking drugs capable of producing acneiform eruptions such as oral or local steroids, vitamin B12, anticonvulsive drugs; and (g) patients with facial dermatoses that could interfere with the evaluation of the study.

Two hundred and five patients with inflammatory acne (comedones, papules and/or pustules) were originally recruited. Ten patients were lost to follow-up or voluntary withdrawal and four patients discontinued the treatment, thus 191 individuals completed the study. Our statistical analysis and evaluation of the combination of 5% benzoyl peroxide-erythromycin 3% efficacy was based on the data collected from 191 patients who completed the study.

Of these patients, 54 were males and 137 females, mean age 17 ± 3.2 and 24.3 ± 8.5 years, respectively (Table 1). Sixty-eight patients had mild acne and 123 had moderate acne at baseline (Table 1).

Topical therapy

The combination of 5% benzoyl peroxide-erythromycin 3% was applied once daily as monotherapy. The dosage scheme included initially a face-cleansing step using the same non-medicated soap (active foam, Frezyderm®, Athens, Greece) and the application of the topical gel 5% benzoyl peroxide-erythromycin 3% as a thin layer on the face including affected and non-affected areas. The topical agent was applied only on the face once daily for 3 months. In addition, patients were advised to avoid the use of the topical agent with dark clothing and were allowed to use non-comedogenic products, for example, make up throughout the study.

Patient baseline characteristics

A total of 191 patients with papulopustular acne completed the study. The majority of patients were female ($n=137$, 71.7% of the sample), while the mean age of the sample (\pm standard deviation) was 22.3 ± 8.1 years (Table 1). Age differed between the two genders (T-test statistic $p<0.001$). On the average, men were seven years younger than women (mean age, 17.2 ± 3.2 and 24.3 ± 8.5 years, respectively).

The mean number of non-inflammatory lesions at baseline was 28.8 ± 11.5 , while the mean number of inflammatory lesions was 15.8 ± 5.5 (Table 2). These

Table 1. Gender and age of the patients. Base: All patients (N=191)

		N	%
Gender	Female	137	71.7
	Male	54	28.3
Age (years) <i>Mean value=22.3±8.1 years</i>	≤22	115	60.2
	>22	76	39.8

Table 2. Mean baseline number of lesions, by gender and age. Base: All patients (N=191)

Baseline number of non-inflammatory lesions	Gender		Age (years)		Total
	Female	Male	≤22	>22	
Mean	27.7	31.5	30.0	26.9	28.8
Std Deviation	10.6	13.2	12.0	10.4	11.5
N	137	54	115	76	191
Baseline number of inflammatory lesions					
Mean	16.8	13.3	15.7	16.0	15.8
Std Deviation	5.8	3.7	5.4	5.7	5.5
N	137	54	115	76	191

Table 3. Statistical parameters for findings analysis

<i>Independent variables:</i>	<i>Tests:</i>
Gender	T-test
Age	Pearson correlation coefficient
Percentage reduction of the inflammatory and non-inflammatory lesions	Spearman's correlation coefficient

findings were statistically significantly different between males and females, as shown in Table 2 (non-inflammatory lesions: multiple linear regression t-statistic $p=0.040$, T-test statistic $p=0.040$; inflammatory lesions: multiple linear regression t-statistic $p<0.001$, T-test statistic $p<0.001$). More specifically, the number of non-inflammatory lesions was greater in men, while the number of inflammatory lesions was greater in women (Table 2).

Assessment of efficacy

The primary outcome utilized for efficacy assessment was the overall mean number of inflammatory and non-inflammatory lesions, expressed as percentage decline from the baseline (week 0-week 12). Each participant's lesions were counted at the beginning (week 0-baseline) and at the end of treatment (week 12).

The secondary outcome included patient satisfaction, i.e. the proportion (percentage) of patients that reported a slight to moderate improvement, significant improvement, or complete cure of their facial acne on a 4-point scale. Each patient was scored on a 0-3 scale (0 = worse or no improvement; 1 = slight to moderate improvement; 2 = significant improvement; and 3 = complete cure).

Any features of local irritation and adverse events identified from the start of the study medication were recorded.

Statistics

Statistical analysis of the baseline characteristics as well as the findings after treatment was carried out using the following methods:

- 1 T-test examined the association of gender with age.
- 2 Multiple linear regression technique (method = stepwise/forward) tested the statistical relation between the baseline number of inflammatory and non-inflammatory lesions (dependent variables) and the variables of age and gender (independent variables).
- 3 Paired sample t-test compared the baseline number of inflammatory and non-inflammatory lesions with the respective values after treatment.
- 4 The same test compared the mean percentage reduction of inflammatory lesions from baseline ($[(\text{baseline number of lesions} - \text{number of lesions after treatment}) \times 100 / \text{baseline number of lesions}]$) with the respective reduction of the non-inflammatory ones.
- 5 Multiple linear regression technique (method = stepwise/forward) tested the statistical relation of the percentage reduction of inflammatory lesions (dependent variable) with the variables of age and gender (independent variables).
- 6 The same technique tested the statistical relation between the percentage reduction of non-inflammatory lesions (dependent variable) and the variables of age and gender (independent variables).

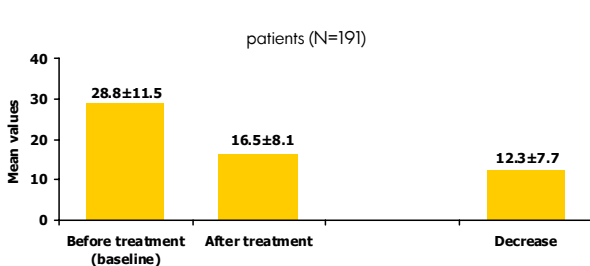


Figure 1. Mean number of non-inflammatory lesions before and after treatment. Base: all patients (N=191).

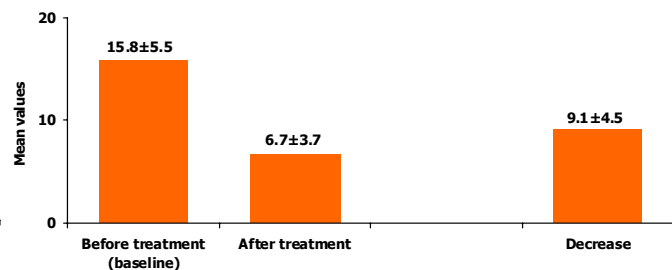


Figure 2. Mean number of inflammatory lesions before and after treatment. Base: all patients (N=191).

Table 4. Number of lesions: Percentage reduction from baseline, by gender and age. Base: All patients (N=191)

Non-inflammatory lesions	Age (years)		Gender		Total
	<=22	>22	Female	Male	
Mean	45.1	37.9	38.9	50.7	42.2
Std Deviation	18.0	19.0	18.2	17.4	18.7
N	115	76	137	54	191
Inflammatory lesions					
Mean	60.4	53.0	53.3	67.9	57.5
Std Deviation	20.5	21.1	20.6	18.3	21.0
N	115	76	137	54	191

7 Finally, the same technique was applied to test the relation of patient satisfaction with treatment (dependent variable) with the variables of age, gender and percentage reduction of inflammatory and non-inflammatory lesions (independent variables) (Table 3).

8 All findings of the linear regression techniques were cross-validated using the following univariate tests

A finding was considered significant if it was traced by both regression and univariate techniques.

reduction of non-inflammatory ones (paired sample t-test, $p < 0.001$). More specifically, the mean percentage reduction of non-inflammatory lesions from baseline was $42.2 \pm 18.7\%$, while the respective percentage for inflammatory lesions was $57.5 \pm 21.0\%$ (Table 4, Fig. 3).

The percentage reduction of inflammatory and non-inflammatory lesions was greater in men than in women (non-inflammatory lesions: multiple linear regression t-statistic $p < 0.001$, T-test statistic p-value

RESULTS

Reduction of inflammatory and non-inflammatory lesions

Upon completion of the study, the mean number of non-inflammatory lesions decreased from 28.8 ± 11.5 at baseline to 16.5 ± 8.1 at the last visit (mean decrease = 12.3 ± 7.7) (Fig. 1), while the mean number of inflammatory lesions decreased from 15.8 ± 5.5 at baseline to 6.7 ± 3.7 at the last visit (mean decrease = 9.1 ± 4.5), as shown in Figure 2. These findings were statistically significant (paired sample T-test, $p < 0.001$ both).

The mean percentage reduction of inflammatory lesions from baseline ([baseline number of lesions – number of lesions after treatment] X100/baseline number of lesions) was greater than the respective

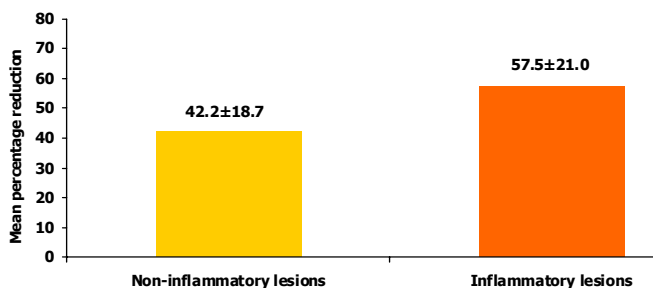


Figure 3. Number of lesions: percentage (%) reduction from baseline. Base: all patients (N=191).



Figure 4. (a) Acne with inflammatory and non-inflammatory features before treatment initiation (baseline) with the topical agent; (b) Acne after topical treatment (week 12). Significant clinical improvement.



Figure 5. (a) Acne with inflammatory and non-inflammatory features before treatment (week 0); (b) Acne with inflammatory and non-inflammatory features after treatment with 5% benzoyl peroxide-erythromycin 3% (week 12).

<0.001; inflammatory lesions: multiple linear regression t-statistic $p < 0.001$, T-test statistic $p < 0.001$).

The mean percentage reduction of non-inflammatory lesions was $50.7 \pm 17.4\%$ in men and $38.9 \pm 18.2\%$ in women, while the mean percentage reduction of inflammatory lesions was $67.9 \pm 18.3\%$ in men and $53.3 \pm 20.6\%$ in women (Table 4, Figs. 4a, b and 5a, b).

Patient satisfaction score

Patient satisfaction with treatment correlated positively with the percentage reduction of inflammatory lesions from baseline (multiple linear regression t-statistic $p < 0.001$ /Spearman's rho correlation coefficient = 0.606, $p < 0.001$) (Fig. 6).

Adverse events

Four patients discontinued their treatment. In three patients, two females and one male, the 5% benzoyl peroxide-erythromycin 3% preparation induced dermatitis that subsided without topical corticosteroids upon cessation of topical medication. The fourth patient, a female, withdrew from the treatment because of poor results after only one month of application. Another patient, a female, mentioned clothing discoloration that did not lead to treatment discontinuation.

No serious adverse events were observed. No photosensitivity, acne aggravation or hypomelanosis in the area of application were noted. The four patients that discontinued treatment belonged to those that did not respond sufficiently to 5% benzoyl peroxide-erythromycin 3% topical preparation (Fig. 6).

In general, the topical agent was well tolerated with limited and transient side effects, usually seen

at the beginning of treatment. The majority of the adverse effects recorded were mild to moderate and did not require treatment discontinuation.

DISCUSSION

Clinical presentation of acne varies depending on the condition severity (7,8). Acne vulgaris is common in teenagers and usually resolves by the age of 20; only a few individuals require treatment in their 30s or 40s. The areas of the skin that are primarily affected include the face, shoulders, upper chest and back (9). The treatment of acne aims to reduce bacterial colonization of the pilosebaceous follicle, reduce the rate of sebum production, reduce inflammation, and remove the keratinized layer that blocks the follicles.

Systemic acne therapy includes the use of oral antibiotics, retinoids and oral contraceptives, depending on the disease severity. In the class of retinoids, oral isotretinoin is the treatment of choice for severe acne (10). Since isotretinoin is a teratogenic agent, pregnancy must be avoided and contraception counseling is mandatory. It may also produce additional problems and patients experiencing its side effects should have their treatment adjusted according to therapy response (11).

Oral antibiotics include oxytetracycline, erythromycin, minocycline, doxycycline, lymecycline or trimethoprim (1). Oral antibiotic therapy may be associated with gastrointestinal disturbance, vaginal candidiasis, pseudomembranous colitis, and in case of tetracyclines vestibular disturbances and phototoxic effects. Furthermore, oxytetracycline may compromise patient compliance to therapy, as it requires no concomitant administration with food and milk in order to increase absorption (12). Oral administration

of erythromycin has been associated with increased systemic adverse effects and resistance of *P. acnes* strains (9). On the other hand, doxycycline and minocycline are considered as second-line treatments, and trimethoprim as a third-line antibiotic option in patients who have failed to respond to alternative antibiotic treatment (13).

The advent of topical therapy has provided alternative treatment schemes in the management of acne. It is a safe substitute administered when: (i) acne is mild; (ii) systemic treatment is contraindicated; and (iii) to reduce the adverse effects of systemic antibiotics and retinoids and offer better patient compliance.

Topical treatments include topical retinoids, benzoyl peroxide alone or in combination with an antibiotic, azelaic acid and topical antibiotics (14). However, one of the major setbacks in the use of topical antibiotics has been the dramatic increase in bacterial resistance over the past 20 years (4,5). Therefore, combination therapies with topical antibiotics (e.g., with benzoyl peroxide, either alternating or as fixed combinations, or alternating with azelaic acid) are now preferred due to the reduction in *P. acnes* resistance, counteraction of new resistant strains and reduction in the risk of resistant *Staphylococcus aureus* colonization (4,15).

In this 12-week study, the primary efficacy results indicated that topical treatment of acne with 5% benzoyl peroxide and 3% erythromycin gel as monotherapy was associated with a significant reduction of inflammatory and non-inflammatory acne lesions, as shown by their mean percentage reductions from baseline by 42.2% and 57.5% for non-inflammatory and inflammatory lesions, respectively (Figs. 3, 4a, b and 5a, b). These findings are in agreement with previously published data obtained from efficacy and comparative studies using the combination of benzoyl peroxide and erythromycin (16-19). On the other

hand, a mean percent reduction of acne lesions from baseline has been reported in randomized controlled studies with other topical acne treatments: for inflammatory lesions 29% to 40% and for non-inflammatory lesions 24% to 40% (20,21).

In our study, patient adherence to treatment was based on their history of treatment application. In terms of safety, no serious adverse effects were observed.

In terms of acne characteristics recorded, including non-inflammatory (comedones) and inflammatory features (papules and pustules), the combination agent (5%) benzoyl peroxide-erythromycin (3%) resulted in a significant reduction in the number of both types of lesions over the 12-week study, as shown in Figures 1 and 2, with a mean decrease in the number of non-inflammatory and inflammatory lesions of 12.3 ± 7.7 and 9.1 ± 4.5 , respectively. More specifically, the percentage reduction of lesions was greater in men than in women, with a mean reduction of non-inflammatory lesions of $50.7 \pm 17.4\%$ in men and $38.9 \pm 18.2\%$ in women, while the percentage reduction of inflammatory lesions was $67.9 \pm 18.3\%$ in men and $53.3 \pm 20.6\%$ in women (Table 4).

Patient satisfaction with treatment was positive, as shown in Figure 6, considering inflammatory lesions and minimal overall dropout rates (only four patients discontinued treatment).

In an efficacy study, combination therapy with benzoyl peroxide and topical antibiotics (e.g., erythromycin) was found to be more effective and better tolerated than the gel vehicle (16). The same results obtained by Gupta *et al.* verified the efficacy of (5%) benzoyl peroxide-erythromycin (3%) treatment in acne vulgaris, showing significant reductions in papules, pustules and comedones. In addition, the 5% benzoyl peroxide-erythromycin 3% combination

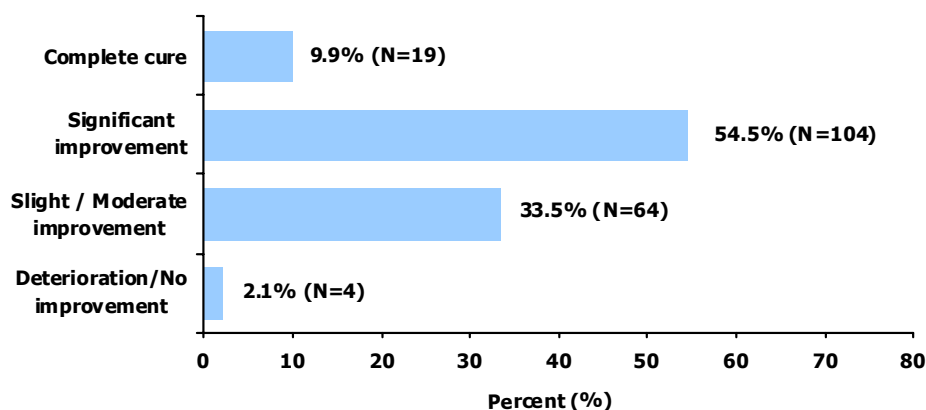


Figure 6. Patient satisfaction with treatment, including patients having completed the study and those who discontinued treatment (N=195).

showed greater decrease in erythema and scaling when compared to 0.025% tretinoin-4% erythromycin gel (17). The combination of 5% benzoyl peroxide and erythromycin 3% was also found more efficacious when compared with topical clindamycin or a combination of 4% erythromycin-zinc 1.2% as topical solution (18,19).

Similar efficacies were, however, observed between 5% benzoyl peroxide-erythromycin 3%, 5% benzoyl peroxide-clindamycin 1%, and 5% and 0.1% isotretinoin-erythromycin 4% for the treatment of mild to moderate acne vulgaris, showing improvement in inflammatory lesions and a lower adverse event profile in case of 5% benzoyl peroxide-erythromycin 3% (22,23).

CONCLUSION

The findings of this study confirmed the use of 5% benzoyl peroxide-erythromycin 3% topical gel to be efficient in the treatment of inflammatory acne, with satisfactory patient compliance and tolerance. This combination topical gel provides a safe alternative to topical treatment and systemic antibiotics, reducing the incidences of *P. acnes* resistance (24).

Acknowledgments

We are indebted to Dr Alexandra Maragkou for her assistance as well as the statistical analyst Panos Katerelos.

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