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TOPICAL ERYTHROMYCIN-ZINC ACETATE COMPLEX LOTION VERSUS TOPICAL ERYTHROMYCIN GEL IN TREATMENT OF MILD TO MODERATE ACNE VULGARIS

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Abstract
Introduction: Topical antibiotics are the main step in the treatment of mild to moderate acne vulgaris. Erythromycin is one of the effective topical therapies for this disease. Zinc sulfate 5% solution was reported to be effective in treatment of acne vulgaris and rosacea.
Aim: To compare the effectiveness and side effects of topical erythromycin in combination with zinc and erythromycin alone in treatment of mild to moderate acne vulgaris.
Material and Methods: This single, blind, therapeutic, comparative study was done in the Department of Dermatology – Baghdad Teaching Hospital, Baghdad, Iraq; from May 2012 - August 2013.Scoring of acne was carried out and the patients were examined every two weeks for 10 weeks of treatment. One month after stopping drugs, patients were evaluated for drug complications and disease recurrence.
Eighty patients fulfilling enrollment criteria were included in this study. Patients were divided into two groups: Group A (40 patients) treated twice daily with topical erythromycin-zinc complex lotion and Group B (40 patients) treated twice daily with topical 2% erythromycin gel.
Results: Both topical erythromycin-zinc lotion and erythromycin gel were statistically an effective therapy starting after 6 weeks treatment and up to 4 weeks after stopping treatment. Erythromycin-zinc lotion was more effective and act earlier than erythromycin gel starting from 4 weeks of therapy till the end of treatment (after 10 week) and even after 4 weeks after stopping the treatment (p value <0.0001).
Conclusions: Erythromycin-zinc complex lotion was an effective and well tolerated topical therapy for mild to moderate inflammatory acne vulgaris and was more effective than erythromycin gel alone.

Key words: acne vulgaris; inflammatory; erythromycin, zinc acetate

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Introduction

The pathogenesis of acne vulgaris is multifactorial. The four major identified factors are: excess sebum production, follicular epidermal hyperkeratinization, the proinflammatory effects of propioni bacterium acnes and other normal skin flora, and inflammation [1].

Many topical agents have been used to target the known pathogenic factors like benzoyl peroxide, topical retinoids, azelaic acid, salicylic acid and topical antibiotics, such as erythromycin, clindamycin, and nadifloxacin. Topical antibiotics are the most commonly used therapeutic agents for the treatment of mild to moderate inflammatory acne [1,2].

Erythromycin is a macrolide antibiotic that has long been used topically for acne. It is one of the most common prescribed topical antibiotics.

Erythromycin has favorable effects in resolving inflammatory acne lesions not only by reducing the *Propioni bacterium acnes* density but also by directly inhibiting neutrophil chemotactic factors and reactive oxygen species production [1-3].

Zinc is a metallic element with bacteriostatic activity against *Propioni bacterium acnes*; it also inhibits neutrophils chemotaxis and reduces tumor necrosis factor production [4]. If used topically, zinc reduces sebum production [5], has keratolytic activity [6], increases tissue healing [7]. It also has anti-oxidant [8], antibacterial [9], antiviral [10], antiprotozoal [11], antifungal [12], immunomodulatary [13], anti-inflammatory activities [14]. If combined with antibiotics, it will reduce antibiotic resistance and increase antibiotic absorption efficiently into the skin [6].

Therefore the present work was arranged to evaluate the effectiveness of erythromycin-zinc complex compared to erythromycin alone in treatment of mild to moderate acne vulgaris.

Material and Methods

This single, blind, therapeutic, comparative study was carried out in the Department of Dermatology – Baghdad Teaching Hospital, Baghdad, Iraq from May 2012 to August 2013.

Eighty patients were included in this study, 19 (23.8%) males and 61 (76.3%) females and their ages ranged from 13-29 years with a mean ±SD of 19.97 ± 3.93 years.

Full history was taken from each patient including: age, gender, duration of disease and previous treatment. Physical examination was done to evaluate the severity of acne

Scoring of severity of acne was carried out by counting the inflammatory lesions (papules and pustules) according to Habif [3]. Side effects were recorded at each visit.

Acne was defined as mild acne in which the count of pustules is less than 20 and the count of papules is less than 10, moderate acne in which the count of pustules is ranging between 20-40 and the count of papules is ranging between 10-30 and severe acne in which the count of pustules is more than 40 and the count of papules is more than 30.

Inclusion criteria into this study were mild to moderate inflammatory acne vulgaris.

Exclusion criteria were severe and nodulocystic acne, and coexistence of any other dermatoses involving the face and allergy to medications, plus patients who had used any topical and systemic treatments in the previous two months, pregnant and lactating women. Patients with other types of acne like drug induced acne, cosmetic acne, post-hair epilation acne, occupational acne, perioral dermatitis, mechanical acne, and acne aestivalis were also excluded.

Formal consent was taken from each patient before starting the trial of treatment, after full explanation for the nature of the disease, course, treatment, prognosis and its complications, the target of the present work regarding the drug, its efficacy, side effects, the method and duration of treatment and follow up. Ethical approval was confirmed from scientific council of Dermatology and Venereology Iraqi Board for Medical Specializations.

Color photographs for each patient were performed by using Sony-digital, high sensitivity, 16.1 megapixel camera in the same place with fixed illumination and distance.

Patients were divided into two groups according to the mode of treatment, Group A treated with erythromycin-zinc complex [(Zineryt)^{R} produced by: Astellas Pharma Europe B.V, Leiderdorp, The Netherlands; which contains erythromycin 40mg and zinc acetate 12mg per ml on concentration] and Group B treated with 2% erythromycin gel [(Erythromycin)^{R} Produced by: Al-Shifa Company, Damascus, Syria, 2% gel].

Patients were instructed to apply the treatment twice daily for 10 weeks. The clinical evaluation was done every two weeks till the end of the ten weeks. Then the patients were asked to stop the use of medication to be re-evaluated again after one month without any treatment to review the relapse rate, local and systemic side effects. Satisfaction of patients to treatment is classified into full satisfaction, partial satisfaction and no satisfaction.

Statistical analysis were done using SPSS version 20 (Statistical Package for Social Sciences). Comparison between both groups was done by using independent sample t-test. Comparison before and after treatment in each group was done by using paired t-test, comparison of reduction rate of the lesions in both groups done by using chi- square, and P-value < 0.05 was considered as level of significance.

Results

The mean ages± SD of patients in Group A were 19.95 ± 3.6 years, 10 were males and 30 were females with female to male ratio 3:1. The mean ages± SD of patients in Group B were 20 ± 4.26 years, 9 were males and 31 were females with female to male ratio 3.4:1.

The mean ± SD of duration of acne in patients within Group A were 18.70 ± 14.50 (range from 4-60 weeks), and the mean ± SD for those in Group B were 16.10 ± 12.66 (range from 4-60 weeks). Both groups were statistically matched regarding age, gender and duration of the disease.

In Group A the papules started to be reduced significantly after 4 weeks of treatment (p value= 0.0001), while the number of pustules started to be reduced after 2 weeks (p value= 0.019). In Group B the papules and pustules started to be reduced significantly after 6 weeks of treatment (p value <0.0146, and 0.0049 respectively).

Comparison of Group A with Group B revealed that reduction in number of papules and pustules was significantly more in Group A starting from the 4th week and increased at each visit till the end of the treatment (Tabl. I; Figs 1 - 2).

The percent reduction rate from baseline visit up to 10 weeks of treatment for Group A were 77.2% and 85.5% for papules and pustules respectively. And for Group B were 35% and 23.25% for papules and pustules respectively (Tabl. II).

After one month of follow up, there was no significant relapse in both groups as the number of papules and pustules did not increased significantly (p value= 0.90 for papules and 0.92 for pustules in Group A, 0.85 for papules and 0.91 for pustules in Group B) (Tabl. III).

The assessment of local side effects for Group A showed: burning sensation in 20 (50%) patients, flare-up at the beginning of treatment 5 (12.5%), erythema 12 (30%), scaling 13 (32.5%), dry skin 30 (75%) and pruritus in 8 (20%) patients. All these symptoms and signs were disappeared after 10 weeks from starting treatment except dry skin which persists in three patients (7.5%).

The assessment of local side effects for Group B revealed: burning sensation in 2 (5%) patients, erythema in 1 (2.5%), scaling in 2 (5%), dry skin in 4 (10%) and pruritus in 3 (7.5%) patients. All these symptoms disappeared after 10 weeks from starting treatment. For both groups, the side effects did not necessitate stopping the treatment.

The assessment of systemic side effects for Group A showed 3 (7.5%) of patients suffered gastrointestinal upset, 1 (2.5%) from headache at 2nd visit. These complain resolved at next visit without discontinuation of treatment. Patients in Group B showed no systemic side effects along the course of treatment.

In Group A; 30 (75%) patients were fully satisfied, 7 (17.5%) patients were partially satisfied and 3 (7.5%) patients were not satisfied. In Group B; 20 (50%) patients were fully satisfied, 10 (25%) patients were partially satisfied and 10 (25%) patients were not satisfied. Hence the patients in Group A were significantly satisfied with treatment more than patients in Group B (p value= 0.043).

	Papules (Mean ±SD)			Pustules (Mean ±SD)		
	Group A	Group B	P value	Group A	Group B	P value
Baseline visit	11.40 ± 4.07	11.50 ± 3.29	0.904	20.58 ± 7.25	19.65 ± 4.88	0.505
After 2 weeks	9.55 ± 4.74	10.82 ± 3.16	0.161	*16.65 ± 7.39	19.00 ± 4.80	0.096
After 4 weeks	*7.32 ± 4.15	10.15 ± 3.29	#0.001	*9.88 ± 4.95	17.98 ± 4.60	#0.0001
After 6 weeks	*5.38 ± 3.93	*9.68 ± 3.25	#0.0001	*6.50 ± 4.91	*16.75 ± 4.03	#0.0001
After 8 weeks	*3.15 ± 3.32	*7.88 ± 2.84	#0.0001	*3.30 ± 3.70	*16.20 ± 4.26	#0.0001
After 10 weeks	*2.52 ± 2.73	*7.38 ± 2.37	#0.0001	*2.90 ± 3.26	*14.98 ± 3.87	#0.0001

Table I. The mean ± SD of papules and pustules in both groups during the course of treatment.

***Statistically different from the 1st visit within the same group (paired t test).**

#Statistically different between both groups (independent t test).

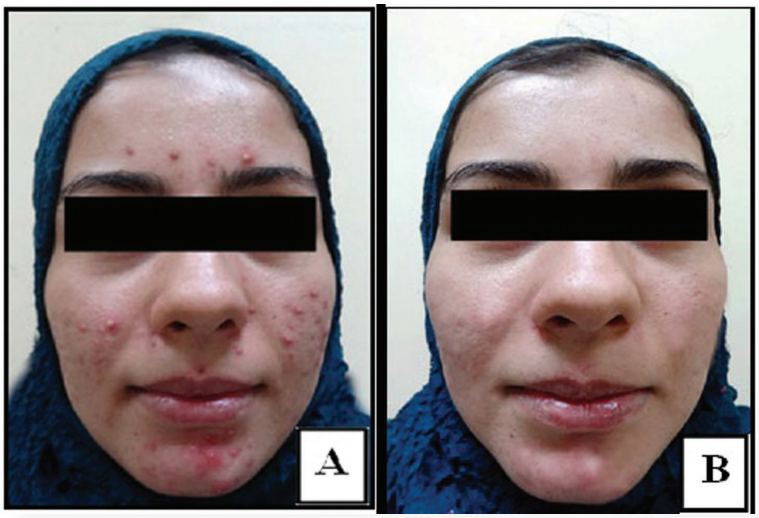

Figure 1. Twenty three years old female with moderate acne vulgaris (A). Before treatment and (B). Complete healing six weeks after treatment with topical erythromycin-zinc lotion.

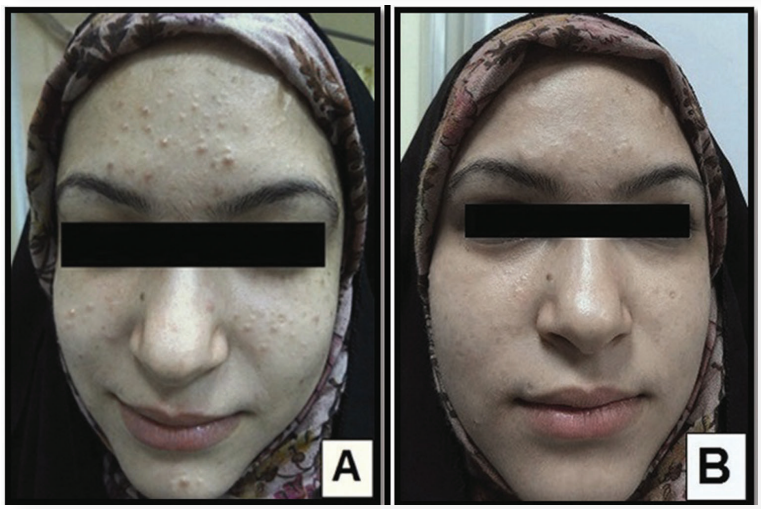

Figure 2. Sixteen years old female with moderate acne vulgaris (A) Before treatment and (B). Complete healing ten weeks after treatment with topical erythromycin gel 2%.

Visits	Group A		Group B	
	Papules	Pustules	Papules	Pustules
(Baseline visit)	0	0	0	0
After 2 weeks	16.2%	19%	6%	3.3%
After 4 weeks	35.8%	52%	11.7%	8.5%
After 6 weeks	52.8%	68,4%	15.8%	14.75%
After 8 weeks	72.36%	84%	31.5%	17.5%
After 10 weeks	77.9%	85.9%	35.8%	23.75%
4 weeks after stopping treatment	77.2%	85.5%	35%	23.25%

Table II. Percent reduction rate for both groups at each visit.

***Percent Reduction = (A-B)/A*100, A is an initial value, B is a final value.**

Group	Type	End of the 10 wks.	4wks following Stopping the R	P-value
Group A	Papules	2.52 ±	2.60 ± 2.82	0.90*
	Pustules	2.90 ±3.26	2.98 ± 3.43	0.92*
Group B	Papules	7.38 ± 2.37	7.48 ± 2.41	0.85*
	Pustules	14.98 ± 3.87	15.08 ± 3.83	0.91*

Table III. Comparison of the number of papules and pustules (mean ±SD) of both groups after one month follow up with that at 10 weeks of therapy.

***p- value not significant ≥ 0.05**

Conclusion

Acne is a common disease and a lot of patients require treatment for relatively long time [1,2]. Topical antibiotics are the main stay for mild to moderate inflammatory acne vulgaris. Erythromycin is widely used antibiotic in acne vulgaris and Zinc sulfate solution 5% has been used successfully in the treatment of acne vulgaris [15].

In present study, the effect of the addition of zinc acetate to erythromycin was assessed. This combination was proved to be effective as the number of papules and pustules were recorded to be reduced significantly from second week onward. Side effects were mild and well tolerated and did not necessitate stopping the treatment. No relapse was recorded after one month follow up.

This study has proved that erythromycin-zinc complex was highly effective in treatment of acne vulgaris, act earlier and much more effective than erythromycin gel alone.

These results are comparable to other studies in which the treatment with Zineryt lotion was found to be more effective than with 2% erythromycin [16], clindamycin lotion [17] and placebo [18,19] as regards the reduction in number of the acne lesions and the severity grade of the acne. There was a significant decrease (77.9%) in inflammatory lesions (papules and pustules) shown for the erythromycin/zinc treatment group at week 8. The reduction rate in other literature for the same period was 69% which is slightly lower than the present study [20].

The mechanism of action of erythromycin in inflammatory acne vulgaris is due to its antibacterial action effects against *Propioni bacterium acnes* and other bacteria that causing acne, while zinc has multiple actions as it has keratolytic [6] anti-oxidant [8], antibacterial [9], immunomodulatary [13], anti-inflammatory [14] and sebosuppressiveactivities [5] and prolong the action of topical antibiotics [6].

In conclusion, erythromycin-zinc complex is highly effective topical combination in treatment of mild to moderate acne vulgaris.

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