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A Survey to Compare the Efficacy of Niosomal Erythromycin Alone versus Combination of Erythromycin and Zinc Acetate in the Treatment of Acne Vulgaris

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Abstract

Background: Acne vulgaris is one of the most common inflammatory skin diseases. Topical antibiotics and retinoids are the first-line therapy in mild to moderate acne vulgaris. Due to increased resistance of Propionibacterium acnes (P. acnes) to topical antibiotics, searching for new formulations of drug release such as niosomes is considered in order to increase efficacy and decrease drug resistance. This study compared the efficacy of niosomal erythromycin4% versus combination of erythromycin 4% and zinc acetate 1.2% in the treatment of mild to moderate acne vulgaris.

Methods: In this double-blind clinical trial, 70 patients with mild to moderate acne vulgaris of both genders aged between 12 to 30 years were included. The patients were evaluated by counting of the lesions and assessment of quality of life during the 2nd, 4th, 8th and 12th weeks.

Results: At the end of the study, 40% and 66.6% of the patients in the niosomal erythromycin group showed a reduction in the number of non-inflammatory and inflammatory lesions, respectively. The percentages for erythromycin and zinc acetate group were 46.6% and 63.3%. One hundred percent of excellent response (8 out of 30 patients) was observed in the niosomal group (P=0.002). A significant improvement in the quality of life was also observed in the niosomal group (P=0.001). Side effects were much less severe in the niosomal group than in the control group.

Conclusion: The results showed that niosomal erythromycin has higher efficacy and less severe side effects in comparison with the combination of erythromycin and zinc acetate.

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Introduction

Acne vulgaris is a chronic inflammatory skin disease affecting the pilosebaceous units in face, chest, and back. It can affect approximately 85% of individuals between 12 to 24 years old (1). Lesions in acne patients are divided into non-inflammatory types (open and closed comedones) and inflammatory (papules, pustules, nodules) (2, 3).

The pathogenesis of acne involves abnormal follicular keratinization, colonization of pilosebaceous duct by Propionibacterium acnes (P. acnes), release of inflammatory mediators such as IL 1, IL8, and IL17, as well as excess sebum production that is induced by androgenic hormones like testosterone and dihydrotestosterone (4-7).

Acne has a significantly negative effect on the quality of life (QoL) and self-confidence of sufferers. Hence, treating the disease at early stages is recommended in order to reduce severity of the lesions and prevent long-term side effects such as scarring and dyspigmentation (8-10).

The choice of the treatment is influenced by the severity of lesions, patient's preference, skin type, drug tolerance, and the presence of comorbidities. Topical retinoids and antibiotics are the first-line of treatment in mild to moderate acne cases (9, 11).

Erythromycin is a macrolide antibiotic with bacteriostatic properties through the inhibition of bacterial protein synthesis. It reduces leukocyte chemotaxis, inhibits the production of pro-inflammatory cytokines, including TNF α, IL1, IL6, and IFNγ by P. acnes. Erythromycin has an anti-inflammatory and mild comedolytic effect (12-14). The side effects of erythromycin are skin dryness, desquamation, erythema, pruritus, and contact dermatitis (15, 16). Due to the high incidence of resistance to the topical antibiotics, it is recommended that erythromycin be combined with other anti-acne medications (17, 18).

Zinc compounds, in addition to immune system regulation, have an anti-inflammatory and bactericidal effect on P. acnes; they also express anti-androgenic properties through inhibiting 5-α reductase. The combination of erythromycin and zinc acetate has been proved to enhance drug release, improve its penetration into stratum corneum, and reduce drug resistance (19, 20).

In order to increase efficacy and facilitate penetration of drugs into the pilosebaceous unit, searching for new formulation of drug release is always needed. Niosomes are made of a hydrated mixture of cholesterol and non-ionic surfactants such as alkyl amides, alkyl ethers, and alkyl esters. Low production cost, easy storage, high stability, as well as slow and controlled drug release are among the advantages of the formulations (21, 22).

The aim of this study was to investigate and compare the efficacy of niosomal 4% erythromycin versus the combination solution of erythromycin 4% and zinc acetate 1.2%.

Methods

The present study is a double-blind randomized clinical trial. Based on the results of the pilot study (the rate of good efficacy in treatment group A and B was 73.3% and 26.7%, respectively), the sample size was estimated as 60 patients with a statistical power of 80%. The inclusion criteria were those 12-35 years old with mild to moderate acne vulgaris.

The exclusion criteria were as follows: pregnant or lactating women, people with known hypersensitivity to erythromycin and zinc acetate, treatment with oral isotretinoin within the last 6 months, oral estrogen compounds within last 3 months, topical retinoid compounds and antibiotics within the last 1 month, patients with hirsutism, androgenetic alopecia, and polycystic ovary syndrome.

After the signing of the consent forms by participants, the questionnaires asking age, gender, location of the lesion, disease duration, and the type of lesion (inflammatory, non-inflammatory) were completed. In the next step; patients were randomized by Minitab 16 (Mini Tab Inc.) into two groups A(niosomal 4% erythromycin suspension) and B (erythromycin 4% and zinc acetate 1.2%). Both drugs were kept in identical amber glass containers, so the evaluating physician and the patient were unaware of the compounds in the containers.

Patients were instructed to apply the drug twice a day in the morning and in the afternoon on cleaned and dried face. Thereafter, the efficacy and side effects of the drugs were investigated during four visits in the 2nd, 4th, 8th, and 12th weeks. The response to treatment was evaluated both by counting the lesions and assessment of QoL (23-25).

The efficacy of treatment based on the percentage of inflammatory and non-inflammatory lesions reduction was defined as follows: Excellent response (76 to 100% reduction of lesions), Good response (51 to 75% reduction of lesions), Fair response (26 to 50% reduction of lesions), and Poor response(less than 25% reduction of lesions) (25).

In order to assess QoL, we used Cardiff Acne Disability Index questionnaire (CADI) containing 5 questions concerning the impact of disease on emotions, social relations, and behavior of patients in the previous month. Each question could be scored from 0 to 3. The total score was the sum of all the question scores that could be from 0 to 15. The higher the score, the more impaired the QoL. Reliability and validity of this questionnaire in Persian version is evaluated with Cronbach's alpha coefficient=0.79 (24).

Included side effects were erythema, pruritus, burning, and desquamation graded from 0 (no side effects) to 3 (severe side effects), assessed in each treatment session by the evaluating physician and questions asked the patients (25). This study was approved by the ethics committee of Kerman University of Medical Sciences with Code No. K / 93 / 369.

Preparation of Niosomes

Niosome formulations were prepared by applying lipid thin-film hydration technique. Sorbitan monostearate 70 % (span 60) and cholesterol 30% molar ratio were used. In order to prepare erythromycin niosomes with this technique, niosome components including nonionic surfactants, cholesterol, and erythromycin (Merck, Germany) were dissolved in 5ml chloroform.

The organic solvent was evaporated with a rotary evaporator in a 100 ml round-bottom flask with temperature of 59°C, under vacuum and with rotation speed of 120 rpm. The total amount of lipid phase for niosome was 200 µmol. In order to ensure the partial evaporation of the solvent, the round-bottom flask was kept in a desiccator for 24 hours. Then, the warm phases (5 ml normal saline) were added to the thin film at a temperature above the phase transition point in the surfactant (60°C). Hydration continued for 30 minutes with rotation speed of 90 rpm in the rotary evaporator. Meanwhile, the sample was continually shaken by hand until a milky white suspension was obtained. The final concentration of erythromycin in formulations was 40 mg/ml.

The formulation properties of niosomes such as particle size, encapsulation percentage, and physical stability were evaluated within the 6 months while being kept in 25°C.

Statistical Analysis

The data were analyzed using SPSS 16 (SPSS Statistics, IBM, Armonk, NY, USA). Descriptive statistical methods were used to determine frequency, relative frequency, and central tendency. The chi-square test was also used to determine drug efficacy and side effects.

Moreover, QoL in both groups was compared using "t test" and the relationship between QoL and drug efficacy was investigated using analysis of variance (ANOVA). The relationship of QoL with age and acne duration was assessed via Pearson test. Drug efficacy over time was determined using Repeated Measure ANOVA.

Results

A) Basic Characteristics

In this study, 70 patients who referred to the Dermatology Clinic of Afzalipour Hospital in Kerman from May- 2014 to June- 2015 entered the study. Finally, 60 patients (30 in each group) completed the study (Algorithm 1). Mean age of the patients in group A and B was 23.66 ± 2. 92 and 24 ±3.37 years old, respectively (p=0.67). Mean duration of the lesion was 1.64 ± 0.79 and 3.04 ± 3.59 years, respectively (p =0.07). There was no significant difference concerning demographic characteristics including age and gender between the two groups. The lowest age of disease onset was 19 and the highest was 34 (Table 1).

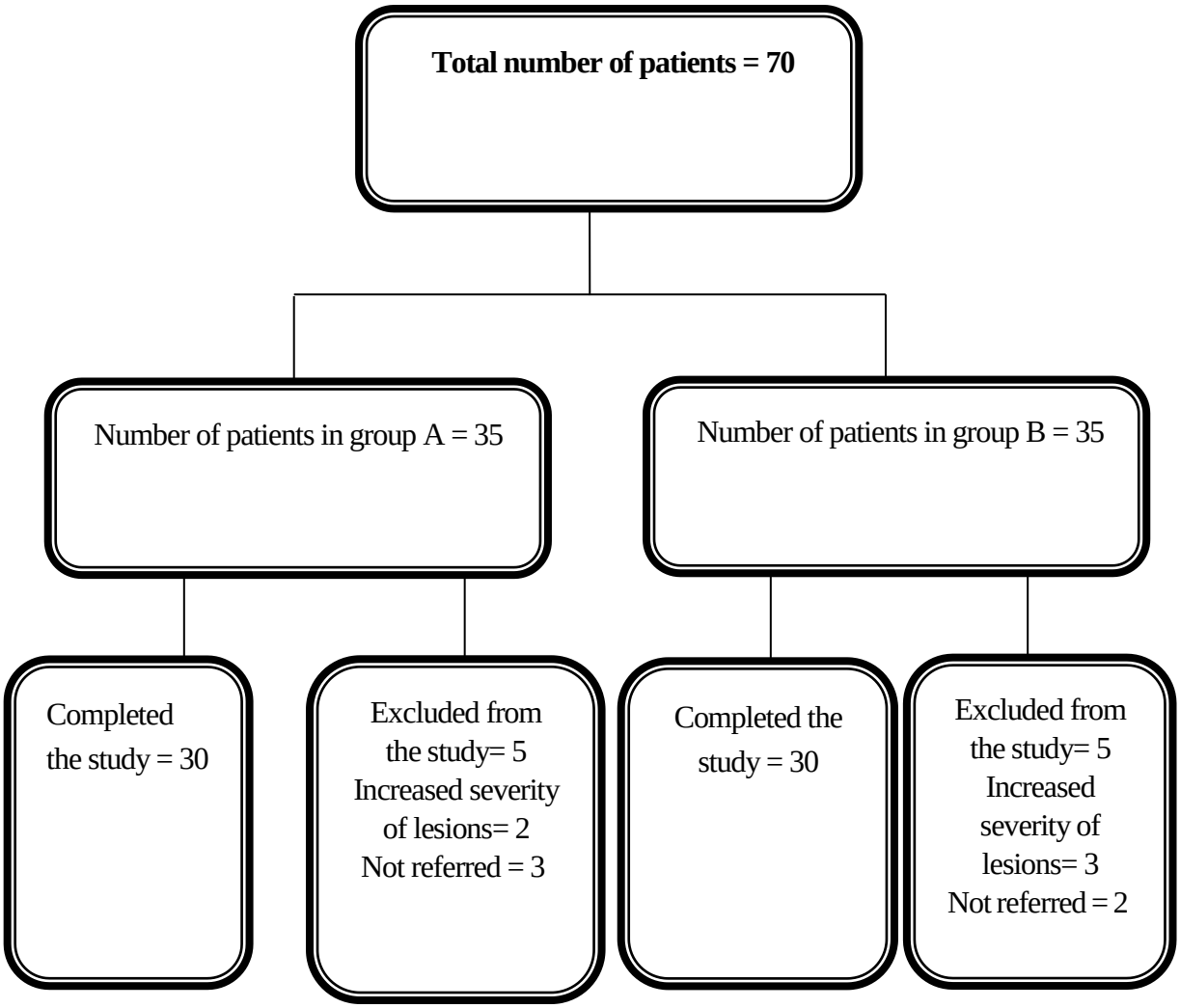

Figure 1. Study algorithm. Group A: Niosomal erythromycin, Group B: Combination of erythromycin & zinc acetate

There was no significant difference between the two groups regarding the severity of acne at the beginning of the treatment (P=0.81). Fifty five percent of lesions were inflammatory (68% papules and 32% pustules) and 45% of lesions were non-inflammatory (65% closed comedones and 35% open comedones). The most common locations of lesions in both groups were cheeks and then forehead (Table 1).

Table 1. Demographic characteristics of the participants

Treatment Variables		A Number (%)	B Number (%)	P Value
Gender	**Female**	5 (55.6)	4 (44.4)	0.71
	Male	25 (49)	26 (51)	
Severity of acne	**Mild**	15 (46.9)	17 (53.1)	0.81
	Moderate	13 (50)	13 (50)	
Location of lesions	**Forehead**	27 (55.1)	22 (44.9)	0.09
	Right cheek	29 (50.8)	28 (49.1)	0.55
	Left cheek	25 (47.2)	28 (52.8)	0.22
	Nose	10 (15.5)	12 (54.5)	0.59
	Chin	9 (50)	9 (50)	0.61

Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

B) Treatment Efficacy

At the end of the study, 40% and 46.6% of the subjects in group A and group B revealed a reduction in the number of non-inflammatory lesions, respectively. Furthermore, 66.6% and 63.3% of the subjects in group A and group B showed a reduction in the number of inflammatory lesions, respectively. Efficacy of treatment in the two groups based on reduction in acne lesions was significant (P=0.002). Rate of excellent response rate (more than 75% reduction in the number of lesions) was observed in 26.6% (8 persons) and 0% of the subjects in group A and group B, respectively (Table 2).

Table 2. Treatment efficacy based on the percentage of reduction in number of lesions

Treatment efficacy rate	A Number (%)	B Number (%)	P Value
Increase in number of lesions	9 (30)	10 (33.3)	0.002
Poor response (less than 25% reduction)	2 (6.6)	7 (23.3)	
Fair response (25 to 50% reduction)	7 (23.3)	2 (6.6)	
Good response (50 to 75% reduction)	4 (13.3)	11 (36.9)	
Excellent response (more than 75% reduction)	8 (26.6)	0 (0)	

Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

In the niosomal group, reduction in the number of acne lesions over time was significant (P=0.04), whereas in the control group, reduction in the number of lesions over time was not significant (P=0.47) (Figure 1-3).

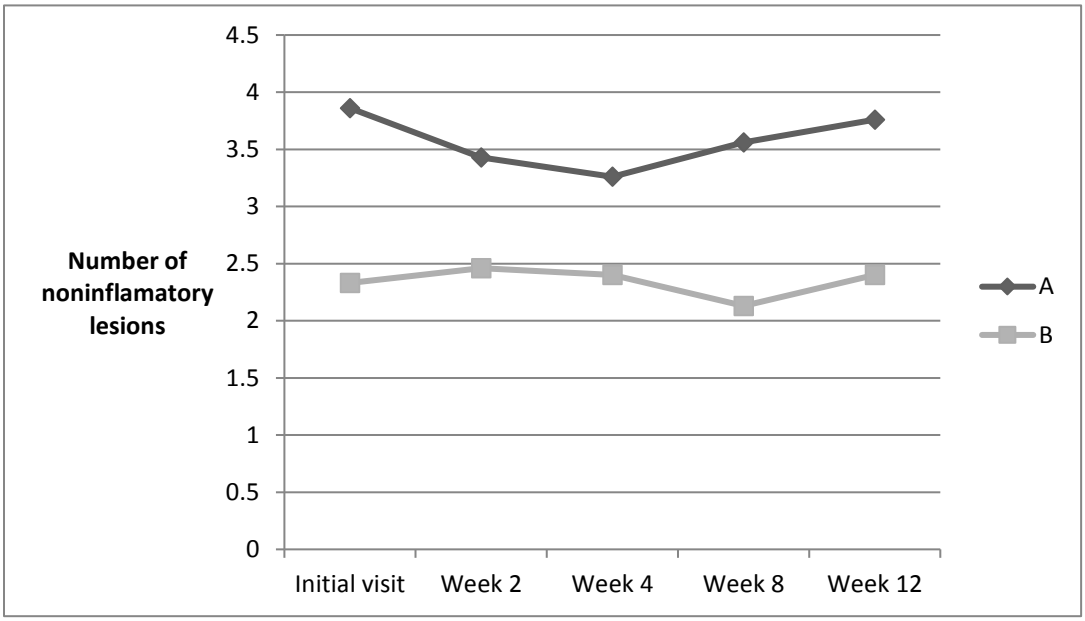

Fig 1. Response to the treatment: Concerning the number of non-inflammatory lesions

Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

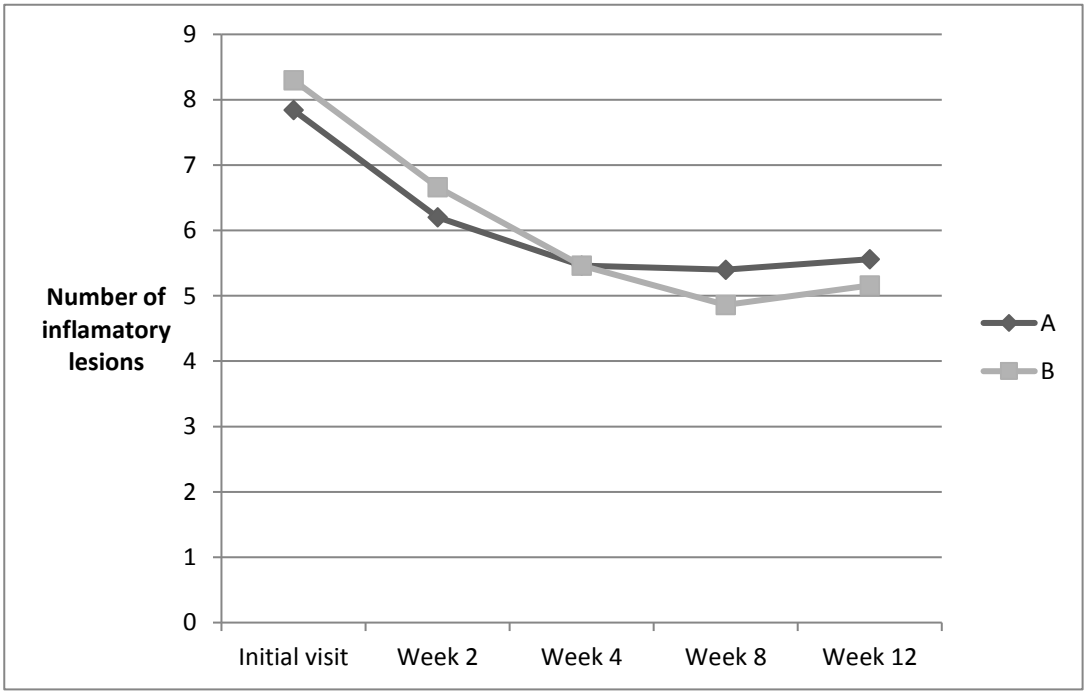

Fig 2. Response to treatment: Concerning the number of inflammatory lesions

Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

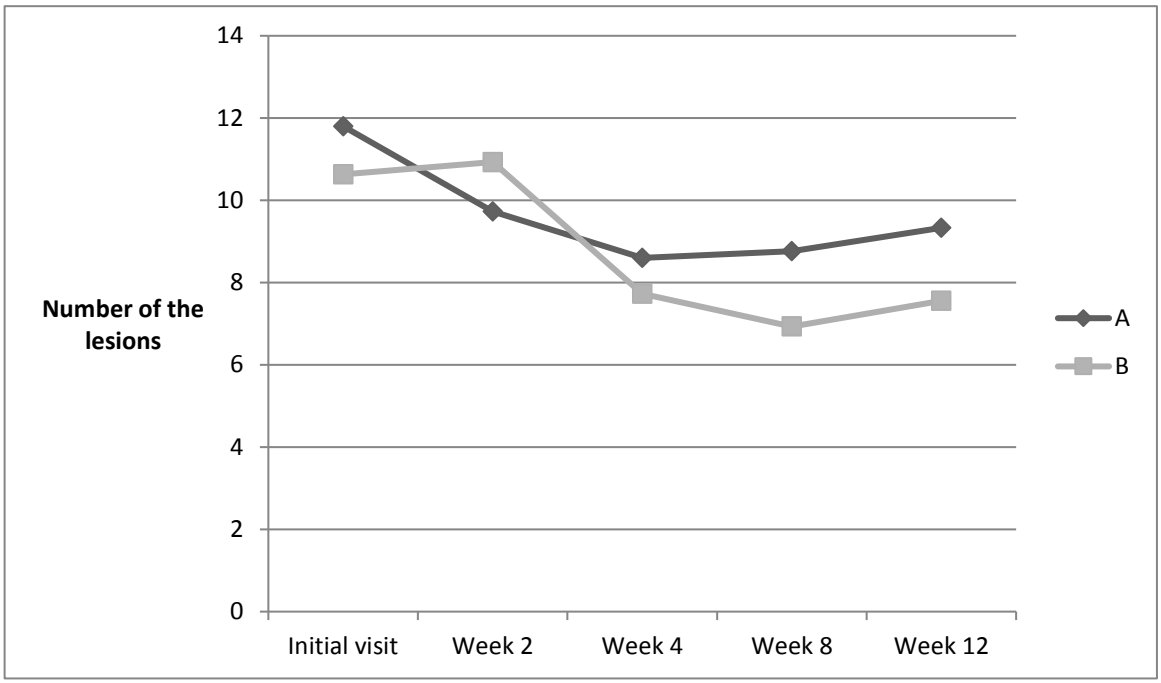

Fig 3. Response to treatment: concerning the number of total lesions

Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

QoL in group A decreased from 8.5± 3.69 before the treatment to 3.64± 2.80 (P=0.022) at the end of the treatment versus 10.5 ± 3.08 and 2.87 ± 1.99 in group B (P=0.038), which was statistically significant. Therefore, improvement in QoL was observed simultaneously with reduction in acne lesions. However, there was no significant difference between QoL and characteristics like age (P=0.78) and acne duration (P=0.86). Improvement in QoL at the end of the treatment was significant in women in comparison with men (P< 0.001).

As presented in Table 3, the severity of side effects such as erythema, pruritus, burning, and desquamation was lower in group A than in group B.

Table 3. Incidence and severity of side effects during treatment sessions

Side effects	Treatment Weeks	Severity	A	B	P Value
Erythema	2nd week	Mild	(53.3) 16	(46.7) 14	*
		Moderate	(46.7) 14	(53.3) 16	*
	4th week	Mild	(59.5) 25	(40.5) 17	0.02
		Moderate	(27.8) 5	(72.2) 13	0.02
	8th week	Mild	(50) 30	(50) 30	*
	12th week	Mild	(50) 30	(50) 30	*
Pruritus & Burning	2nd week	Mild	16 (72.7)	6 (27.3)	0.00
		Moderate	14 (36.8)	24 (63.2)	0.00
		Severe	0(0)	1 (100)	*
	4th week	Mild	28 (54.9)	23 (45.1)	*
		Moderate	2 (25)	6 (75)	*
	8th week	Mild	30 (50)	30 (50)	*
	12th week	Mild	30 (50)	30 (50)	*
Desquamation	2nd week	Mild	29 (58)	21 (42)	0.00
		Moderate	1 (10)	9 (90)	0.00
		Severe	0(0)	1(100)	*
	4th week	Mild	30 (52.6)	27 (47.4)	*
		Moderate	0(0)	2(100)	*
	8th week	Mild	30 (50.8)	29 (49.2)	*
		Moderate	0(0)	1 (100)	*
	12th week	Mild	30 (50)	30 (50)	*

* Results were not significant
Group A: Niosomal erythromycin
Group B: Combination of erythromycin & zinc acetate

Discussion

Antibiotics have a role in the treatment of acne lesions through anti-inflammatory effects and inhibition of P. acnes growth. Based on the severity of acne, these compounds can be used topically or systemically (14).

Systemic antibiotics have a higher efficacy due to adequate distribution and penetration into the follicle. Nevertheless, some patients are not able to take these compounds because of their side effects such as gastric intolerance and vaginal candidasis. (11).

The advantage of using topical antibiotics is limited systemic absorption (less than 10%), which leads to less drug interactions and systemic side effects (26). Modern drug delivery systems like niosomes can lead to better penetration and higher stability of drugs in the pilosebaceous unit due to vesicular structure and smaller particle size. Thus, they lead to a higher drug efficacy, fewer side effects, and less bacterial resistance (21, 22).

The present study compared the efficacy of niosomal 4% erythromycin versus erythromycin 4% and zinc acetate 1.2%. In this study, all the patients who showed more than 75% reduction of acne lesions were in the niosomal group (P=0.002). In both groups, in spite of the decline in the number of acne lesions at the first few weeks of treatment, a slight increase in the number of the lesions was observed at the end of the treatment, which can be due to poor adherence of the patients to the treatment and low compliance. In addition, the efficacy of the drug in both treatment groups was better in inflammatory lesions than in non-inflammatory lesions. This can be due to stronger anti-inflammatory effect compared with the comedolytic effect of topical antibiotics.

So far, a number of studies have been carried out concerning the efficacy of topical antibiotics. However, due to

the high incidence of Propionibacterium resistance in the past two decades, the results cannot be extended.

In one study conducted by Stain Forth and colleagues, the efficacy of erythromycin 4% lotion and zinc acetate 1.2% was compared with oral minocycline. It was concluded that topical antibiotic solution was significantly effective in reducing inflammatory and non-inflammatory lesions. therefore, they recommended the use of topical antibiotics as the first-line treatment for mild to moderate acne in order to reduce side effects and drug resistance (11).

Another study was performed by Chu and colleagues in 1997 on 72 patients suffering from acne. In this study the efficacy of erythromycin 3% gel and benzoyl peroxide 5% was compared with combined erythromycin 4% and zinc acetate 1.2% solution for 10 weeks. Ninety one percent of patients in the erythromycin and benzoyl peroxide group (vs. 48% of patients in the erythromycin and zinc acetate group) revealed at least 50% improvement (19).

In the present study, 39.9% of the patients in the niosomal group (vs. 36.6% in control group) showed at least 50% improvement. The lower response rate in the present study in comparison to Chu's study can be due to increase in P. acnes resistance to antibiotics in the past 2 decades. In Chu's study, 4 patients in the erythromycin and zinc acetate group showed side effects such as dryness, pruritus, erythema, and local irritation. In the present study, side effects were more common than the study by Chu, which can be due to the difference in skin barrier resistance and geographical conditions of the two studies.

In the present study, comparison of side effects between 2 treatment groups showed that the niosomal group has less severe side effects, which are due to better drug tolerance in the niosomal group in comparison with the control group, which may lead to increased compliance in taking drugs by patients. Moreover, in this study, the severity of side effects reduced over time in both groups which was due to improvement in drug tolerance in patients over time. Thus, in order to reduce side effects, we suggest taking drugs less frequently and for a shorter time during the initial weeks of treatment.

In this study, we used QoL to evaluate patients' satisfaction with treatment. A reduction in the number of acne lesions led to better QoL. These results were compatible with previous studies (8). Furthermore, we observed that the improvement in Qol in women was significantly higher than it was in at the end of the treatment compared with baseline visit. This can be explained by more attention of women to cosmetic issues than men.

In this study, there was no significant relationship between QoL and characteristics like age and acne duration. Nonetheless, in previous studies, it was revealed that higher age and longer acne duration can negatively affect QoL (14-16,19). This difference can be due to the small sample size of the present study.

The strengths of this study include randomization and assessing QoL in addition to counting the number of lesions for evaluation of treatment response rate. The main limitations of this study were small sample size and lack of evaluation of drug resistance rate.

It is recommended that other studies be carried out with a larger sample size to investigate the efficacy of niosomal erythromycin and to assess P. acnes resistance to such formulation.

Conclusion

In general, niosomal erythromycin has higher efficacy and less severe side effects as compared with the combination of erythromycin and zinc acetate. Therefore, this drug can be used as an effective and tolerable treatment for patients with mild to moderate acne.

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