

## Comparison of efficacy of Azithromycin vs. Clindamycin and Erythromycin in the treatment of mild to moderate acne vulgaris

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### ABSTRACT

**Objective:** Acne vulgaris is a prevalent inflammatory skin disorder. Topical solutions of clindamycin and erythromycin are the most common treatment in the patients. This study was conducted to compare the effect of topical solution azithromycin as a new method of treatment against topical solutions of clindamycin and erythromycin.

**Methodology:** A randomized double-blind clinical trial was carried out for 20 weeks at the outpatient clinics of Boo-Ali Sina Hospital in Sari (Iran) on 96 patients with mild to moderate acne vulgaris. They were randomly divided in three groups who were matched together based on Acne Severity Index(ASI) and were treated with 2% alcoholic solution of azithromycin, erythromycin and clindamycin respectively twice daily for 16 weeks. Treatment efficacy was determined by Total acne Lesion Counting (TLC).

**Results:** For each three treatment groups, decreased TLC and ASI were significant at the end of 16 weeks ( $P<0.05$ ). Azithromycin was more effective than the clindamycin and erythromycin for acne therapy after 16 weeks ( $P<0.05$ ). Twenty patients (20.8%) of azithromycin group (12.5%) reported to have adverse effects, such as erythema and/or pruritus ( $P<0.05$ ).

**Conclusion:** Topical solution azithromycin is a more effective treatment for mild to moderate acne vulgaris comparing to clindamycin and erythromycin, but it has more local side effects.

**KEY WORDS:** Acne vulgaris, Azithromycin, Clindamycin, Erythromycin, Treatment.

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### INTRODUCTION

Acne, an inflammatory skin disorder, is one of the most common skin diseases treated by dermatologists.<sup>1,2</sup> Early treatment of acne is necessary to

prevent facial scarring and consequently avoiding psychological distress.<sup>3</sup> Topical antibiotics are commonly prescribed to treat mild to moderate acne for the thirty years. The two most commonly used topical antibiotics are clindamycin and erythromycin that reduce the levels of *Propionibacterium acnes* (*P. acnes*) and decrease inflammation.<sup>2,4-6</sup> Some antimicrobial agents such as Benzoyl peroxide have no anti-inflammatory effect but used to treat mild to moderate acne, specially in combination therapy with erythromycin or Clindamycin to minimize the development of resistance. However, because of the emergent of antibiotic-resistant strains, these antibiotics are becoming less effective.<sup>7</sup>

Azithromycin is a newer macrolide with widely tissue distribution and cellular concentration.<sup>8</sup> Azithromycin shows activity against gram-positive, Gram-negative aerobic bacteria and anaerobic

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sepsis, including propionibacterium (*P. acnes*) with minimal side effects and better compliance.<sup>9,10</sup> But there isn't any study about topical solution of azithromycin for treatment of acne.<sup>8</sup> So we conducted this study to compare the efficacy and safety of topical Alcoholic Solution Azithromycin (ASA) versus Alcoholic Solution Erythromycin (ASE) and Alcoholic Solution Clindamycin (ASC) in the treatment of mild to moderate acne vulgaris.

## METHODOLOGY

**Study design:** This was a randomized double-blind clinical trial of three groups comparison, using alcoholic solution 2% of erythromycin(ASE), clindamycin(ASC) and azithromycin(ASA). Ninety-six patients with mild to moderate acne were selected among patients referred to clinic of dermatology at Boo-Ali Sina Hospital in Sari (Iran). This study was approved by the appropriate regulatory and ethics committees in Mazandaran University of Medical Science.

**Patients:** Male and female patients aged 12-28 years with mild to moderate acne vulgaris of the face were eligible. Patients who were using any kind of acne treatment in the previous month were excluded. Subjects using drugs induced acne and female with polycystic ovarian syndrome were excluded. The patients were randomized to each treatment in equal numbers. The patients applied the medication twice daily. The patients were assessed at (day 1) and the end of 2, 4, 8, 12, 16 and 20 weeks after the beginning of study. To maintain blinding, a pharmacist was responsible for dispensing study medication and for instructing the patient on the proper method of application. The scheduled treatment period was 16 weeks and patients were followed at the end of 20 weeks after the beginning of treatment.

**Study treatment:** Patients in azithromycin group received alcoholic solution 2% azithromycin (in 60% ethanol/40% water solution) as the method of Mc Hugh et al.<sup>8</sup> and the other groups received commercial preparation of 2% erythromycin or clindamycin alcoholic solutions obtained from Pakdarou pharmaceutical company in Iran.

**Assessment:** Treatment efficacy was determined by total lesion counts of the whole face. In each visit, the physician assessed global change from baseline as follow: a reduction of 80% or more was labeled good, 50-79% moderate, 20-49% mild, and a reduction less than 20% labeled poor. Adverse events were recorded throughout the study upon the complain of patients. All assessors were blinded to the treatment received. To optimize consistency of subjective

Table-I: Demographic Characteristics.

	Azit	Eryth	clinda	P-value
<b>-Sex</b>				
Male	4(12.5%)	4(12.5%)	4(12.5%)	NS
Female	28(87.5%)	28(87.5%)	28(87.5%)	
<b>-Age(years)</b>				
Mean±SD	18.9±2.9	19.3±2.9	20.4±4.3	NS
Range	15-26	16-25	12-28	
<b>-Family history</b>				
Positive	21(65.5%)	17(53.1%)	18(56.3%)	NS
Negative	11(34.5%)	15(46.9%)	14(43.7%)	
<b>-BMI</b>				
Mean±SD	22.3±3.7	23.1±5.4	22.7±4.4	NS
Range	18.6-31.0	16-38	13-30	

Azit: Azitromycin Eryth: Erythromycin, Clinda: Clindamycin  
BMI: Body Mass Index, NS: Non Significant

evaluations, the same staff saw the same patients at each of their visits.

**Statistical analysis:** Data were analyzed by SPSS software, using ANOVA, Tukey and the other useful statistical methods with  $P < 0.05$ .

## RESULTS

In total, 96 patients (32 patients in each group) were randomly selected to treat and were assessed in March 2006 to December 2007. There were no significant differences between the groups in demographic characteristics and basal non-inflammatory and inflammatory lesion counts (Tables-I, II).

The results from this study show improvement in both the non inflammatory and inflammatory lesions of acne over 16 weeks of treatment period with the three kinds of topical antibiotics. A significant difference in total count of non-inflammatory lesion and total lesion count between three treatment groups is shown in Figs.1 and 2 and Table-II. In the first four weeks of treatment the best response was observed from ASE and from week four onwards the best therapeutic response was observed from AEA. The least effect was observed from ASC.

In our study 20.8% of all patients complained of erythema, pruritus, burning and edema which was more in azithromycin group (12.5%,  $P < 0.05$ ) (Table-III).

## DISCUSSION

The results from this study show improvement in both the non inflammatory and inflammatory lesions of acne over 16 weeks of treatment period with the three kinds of topical antibiotics. Oral and topical antibiotics are the most commonly used for acne lesions. The mechanisms by which antibiotics work

Table-II: Absolute Lesion Count.

	Azit N=32 Mean(SD)	Eryth N=32 Mean(SD)	Clinda N=32 Mean(SD)	One way ANOVA A-E-CP-Value	Tukey test		
					A vs E P-Value	A vs C P-Value	E vs C P-Value
<i>Total number of inflammatory lesions</i>							
Week 0	47.9 (56.1)	65.7 (47.1)	54.7 (34.3)	NS	NS	NS	NS
Week 2	21.7 (23.7)	23.2 (13.7)	29.1 (24.9)	NS	NS	NS	NS
Week 4	15.7 (16.5)	18.2 (12.3)	20.1 (20.2)	NS	NS	NS	NS
Week 8	10.3 (9.1)	13.0 (8.5)	16.4 (16.8)	NS	NS	NS	NS
Week 12	7.1 (7.8)	9.8 (7.8)	12.1 (13.2)	NS	NS	NS	NS
Week 16	5.3 (8.3)	12.0 (12.6)	13.0 (12.2)	NS	NS	NS	NS
Follow up 20 Weeks	5.5 (9.0)	12.8 (16.7)	12.7 (9.9)	NS	NS	NS	NS
<i>Total number of non-inflammatory lesions</i>							
Week 0	148.9 (57.6)	142.7 (50.2)	11.3 (45.9)	NS	NS	NS	NS
Week 2	113.3 (45.9)	101.3 (31.3)	117.9 (34.9)	NS	NS	NS	0.044
Week 4	83.6 (43.7)	79.0 (25.9)	98.4 (39.5)	0.011	NS	NS	0.009
Week 8	62.3 (30.1)	71.3 (22.0)	84.2 (38.4)	0.005	NS	0.008	0.022
Week 12	47.2 (24.9)	57.1 (21.4)	71.2 (33.9)	0.015	NS	0.012	NS
Week 16	38.2 (24.7)	54.8 (26.3)	70.0 (41.1)	0.014	NS	0.010	NS
Follow up 20 Weeks	33.6 (26.7)	52.3 (28.9)	72.6 (38.9)	0.000	NS	0.000	0.005
<i>Total number of lesions</i>							
Week 0	146.8 (96.9)	268.5 (39.4)	215.0 (49.2)	NS	NS	NS	NS
Week 2	135.0 (54.1)	124.6 (38.1)	147.0 (55.5)	NS	NS	NS	0.047
Week 4	99.3 (51.6)	97.2 (33.0)	118.6 (51.5)	0.017	NS	NS	0.015
Week 8	72.7 (32.1)	84.3 (25.3)	100.6 (40.6)	0.005	NS	0.008	0.023
Week 12	54.3 (27.2)	67.0 (24.3)	83.4 (43.3)	0.013	NS	0.010	NS
Week 16	43.6 (27.3)	66.9 (36.1)	83.0 (50.1)	0.013	NS	0.009	NS
Follow up 20 Weeks	39.2 (31.0)	65.2 (43.6)	85.3 (44.4)	0.000	NS	0.000	0.014

NS: Non Significant    Azit: Azithromycin    Eryth: Erythromycin    Clinda: Clindamycin

in acne, varies with the drug. Some medications may have anti inflammatory or antibacterial properties, whereas other medications possess both properties.<sup>8,11,12</sup> The useful affect of 2% Alcoholic solution of the most common antibiotics such as Erythromycin and Clindamycin have showed in various studies.<sup>5,6,8,11</sup>

Oral and topical erythromycin and clindamycin have significant effect in patients with papulopustular acne that comparable with placebo and vehicle.<sup>13-15</sup>

Two randomized double blind clinical trial showed that the efficacy of erythromycin and clindamycin are the same for treatment of acne.<sup>16,17</sup> Clinical isolated of *P.acnes* are known to be highly susceptible to azithromycin.<sup>2,18</sup>

Our study showed the significant effect of all topical medications on inflammatory lesion of acne but the efficacy of erythromycin for the treatment of comedon in the first few weeks was better but from week four onwards azithromycin showed more significant effect on comedon than the other drugs.

Table-III: Side effects detected during treatment.

Drug Side effects	Azithromycin N=32	Erythromycin N=32	Clindamycin N=32	Total N=96
Itch (P=0.002)	10(31.3%)	1(3.1%)	2(6.3%)	13(13.5%)
Erythema (P=0.007)	10(31.3%)	1(3.1%)	4(12.5%)	15(15.6%)
Burning (P= 0.031)	7(21.9%)	2(6.3%)	1(3.1%)	10(10.4%)
Edema (P=0.005)	5(15.6%)	0(0%)	0(0%)	5(5.2%)

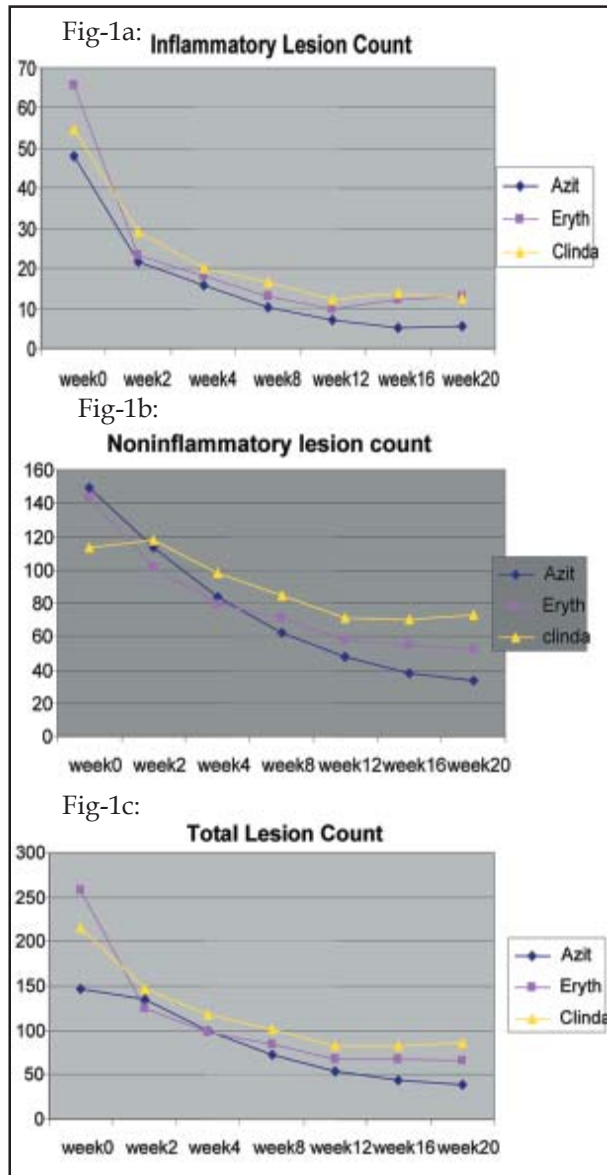


Fig-1: The median percentage reduction. In lesion counts from baseline.

- 1a: Inflammatory lesion count,
- 1b: Non Inflammatory lesion count,
- 1c: Total lesion count.

Differences between groups were tested using the Wilcoxon test.

Azithromycin is a newer macrolide that was developed to overcome the shortcomings of erythromycin, such as gastrointestinal intolerance and short half life.<sup>19</sup> Recently azithromycin was found to be effective in the treatment of inflammatory acne.<sup>10,15,20</sup> The anti inflammatory action of macrolides has been shown in various studies. The results of some studies indicate that macrolides affect several

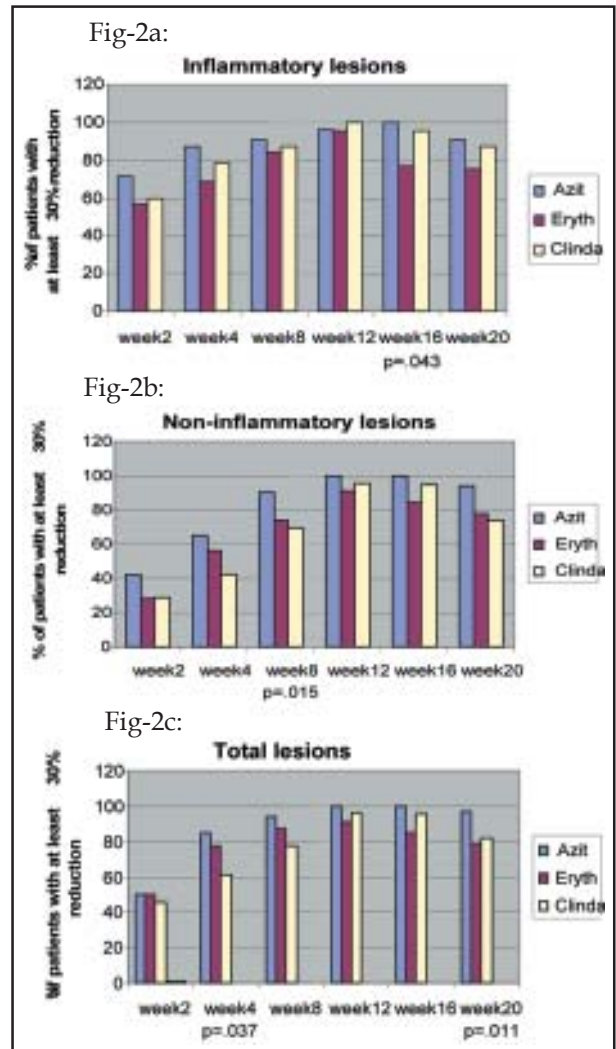


Fig-2: The percentage of patients with a 30% improvement or greater from baseline.

- 2a: Inflammatory lesions,
- 2b: non-Inflammatory lesions,
- 2c: Total lesions.

\*Statistically significant difference after Bonferroni correction (Fisher exact test).

inflammatory processes such as migration of neutrophils, the oxidative burst in phagocytes and production of pro-inflammatory cytokines.<sup>21-23</sup> Azithromycin is a new macrolide which has a unique and superior pharmacokinetic profile when compared with other macrolides. It penetrates tissues rapidly, where it remains for prolonged periods and allow less frequent dosage. Steady-state tissue levels are substantially increased in relationship to serum levels. Azithromycine has also no major drug interactions.<sup>8,10,19</sup> Kus et al showed oral azithromycin decrease the non inflammatory acne lesions as well

as the inflammatory lesions which are comparable to our results, and azithromycin is at least as effective and safe as doxycycline in acne treatment and is a good alternative for those patients who cannot tolerate the side effects of tetracyclines.<sup>24,25</sup>

In our study 20.8% of all patients complained of erythema, pruritus, burning and edema which was more in azithromycin group (12.5%,  $P < 0.05$ ).

Tetracyclines are the first-line antiacne antibiotics.<sup>9,26</sup> However tetracyclines may be associated with a fairly large number of adverse effects. Comparative clinical trials have shown that azithromycin's tolerability profile is superior to conventional antiacne treatment such as erythromycin and doxycycline.<sup>10,15,24</sup> But the concern in use of oral antibiotics is the potential transfer of antibiotic resistance to other organisms.<sup>7</sup>

In order to diminish the risk of resistance emerging, oral antibiotics should not be used in mild acne where topical agents may be sufficient.<sup>27</sup> Topical azithromycin is a promising agent in the treatment of acne and has durable effect, but upon our study's results, topical azithromycin has local side effects and further controlled studies comparing the effectiveness and tolerability of topical azithromycin with conventional antibiotics are suggested.

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