

Comparison of Topical Azithromycin and Clindamycin in the Treatment of Mild to Moderate Acne Vulgaris

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Abstract

Background: Acne vulgaris is the most common cause for dermatology visits and is one of the most common diseases that people experience during their lives. Although this disease is not life-threatening, it may affect the life quality of the patients because of developing irreparable complications on the skin. Dermatologists are in agreement about topical treatment in the mild to moderate acne vulgaris, but extensive using of topical antibiotics and drug resistance have decreased their therapeutic benefits. In this study, we tried to compare the therapeutic effects of topical azithromycin and clindamycin.

Methods: This study was designed and performed as a double blind, randomized clinical trial. Thirty two patients with mild to moderate acne were treated with azithromycin and 30 patients, who were matched with the former group based on age, sex and severity of the disease, were treated with clindamycin for 12 weeks and results of their treatment were compared with each other.

Results: results of this study showed that ratio of response to treatment and decreasing the grade of the disease and number of nodules, papules and pustules were not significantly different in the first month of the treatment in both groups while just the number of nodules in the group on azithromycin showed more decrease in the last months of treatment in comparison with clindamycin (0.88 ± 0.75 vs. 0.25 ± 0.75 , $p=0.015$). Also, clindamycin had more side effects, but the rate of satisfaction with both drugs were high and showed no difference. In this study, no significant association was found between sex and response to treatment and evaluation of association between age and response to treatment showed a significant reverse association between age and decreasing the number of pustules ($p=0.002$, $r = -0.492$).

Conclusion: sum of findings in this study show that topical azithromycin is an effective antibiotic with acceptable side effects and high degree of satisfaction in patients and it can be used for the treatment of mild forms of acne. (*Iran J Dermatol 2008;11:67-72*)

Keywords: acne vulgaris, azithromycin, clindamycin

Introduction

Acne vulgaris is the most common cause of referring to dermatologists and it is estimated that 85- 100% of people experience it during their life¹⁻³. Although this disease is not life – threatening, but because of developing irreparable complications on the skin, it might affect quality of life in patients and consequently have had physical, psychological and social problems during adolescence and adulthood.^{4,5}

Acne manifests as comedonal lesions and or inflammatory lesions such as papules, pustules, nodules and cysts and mostly involves face and trunk.⁶⁻⁸ The main mechanisms of developing acne are sebum production, increased proliferation of corneous cells, bacterial colonization and inflammatory reactions.^{4,5} In contrary to general opinion, with early diagnosis and correct treatment, acne might be treated before the formation of scars on the skin and causing psycho-social problems.^{9,10} So, there are a lot of therapeutic modalities in the forms of systemic and topical and

selecting the type of treatment depends on the type of lesions¹. Topical antibiotics can be used for the treatment of mild to moderate forms or as an adjunctive therapy along with systemic therapy in the moderate forms of acne^{1,6}. Benefits of using topical antibiotics are fewer side effects due to the systemic treatment and decreasing drug resistance and giving patients the opportunity to use an antibiotic with minimum side effects for a longer duration¹¹⁻¹⁵. Clindamycin, in form of hydro alcoholic solutions, has been used as a topical antibiotic in the treatment of acne for approximately 2 decades and its new formulations in the forms of gel and hydrophilic lotions are less irritant⁷. This drug decreases the colonization of propionibacterium acnes and shows its anti-inflammatory effects directly by inhibiting chemotaxis of neutrophils⁷.

However, extensive use of topical and oral clindamycin has resulted in increasing clindamycin-resistance microorganisms which has increased inappropriate therapeutic responses¹². Therefore, other antibiotics such as azithromycin have been introduced for the treatment of acne^{10,11}. Long half life, few side effects and interactions with other drugs and safety in pregnancy have all made azithromycin a popular drug with dermatologists^{9, 10}.

The aim of this study was to compare the therapeutic effects of topical clindamycin with azithromycin in the treatment of mild to moderate acne in terms of severity of acne, number of the lesions, patients' satisfaction and their side effects.

Patients and Methods

This study was designed and performed as a double blind, randomized clinical trial. Thirty two patients were treated with azithromycin and 30 patients with clindamycin. Block randomization method was used for selecting patients. Patients in the azithromycin group received alcoholic solution 2% of the mentioned drug, manufactured by the physiology laboratory of Iran University of Medical Science, every morning and night, and patients in the clindamycin group received alcoholic solution 1% of clindamycin, manufactured by the same laboratory, every morning and night. Duration of treatment was 12 weeks in both groups and along with the aforesaid drugs; topical adapalene gel 1% was prescribed for both groups to be applied at night. Also, it was recommended to both groups to rinse their skin with water and soap and then dry it before applying solutions and then rub the solution on all parts of the skin (and not only on the

lesions) and not to use other topical drugs (other than sun screens and moisturizers) during the course of treatment.

Inclusion criteria were as follows: age ranging from 12 to 40 years, mild to moderate forms of acne vulgaris with at least 10 inflammatory lesions on the face (with at least 3 nodules), a written consent for participation in the study and agreement on following drug orders. Exclusion criteria were having more than 3 nodulocystic lesions, suffering from other forms of acne such as acne conglobata, fulminans and acne secondary to pregnancy or lactation, suffering from other skin diseases such as psoriasis, dermatitis, papulopustular rosacea that affect the therapeutic course, acne on the trunk primarily or predominantly, presence of a systemic disease, pregnancy, lactation, history of allergic reaction to prescribed drugs, receiving NSAIDs in the week before beginning the treatment, being on OCP for less than 3 months, applying topical anti acne drugs within 2 weeks before the beginning of the study, oral drugs in the past month, receiving Accutane within 6 months before the beginning of the study and taking drugs such as theophyllin, phenytoin, barbiturates, carbamazepine, cyclosporine, warfarin, ergotamine and triazolam within one week before beginning the study.

Primary visit of the patients was performed by a dermatologist. Photographs were taken for all patients before beginning the treatment and their lesions were counted according to Leeds system and the severity of their disease was determined. Then, at the end of the 4th, 8th and 12th weeks, second, third and fourth visits were done with photography, lesions were counted and severity of the disease was evaluated. In this study evaluation of response to treatment was according to Leeds system.

After collecting data from all patients, SPSS version 15 was used for data analysis. In this study, level of statistical significance was considered 0.05.

Results

Thirty two patients (34.4% males (11 patients) and 66.6% females (21 patients)) with a mean age of 22.18 ± 6.1 years were assigned to azithromycin group and 30 patients (26.7% males (8 patients) and 73.3% females (22 patients)) with a mean age of 22.97 ± 6.14 years were assigned to clindamycin group. There was no significant difference regarding age and sex in both groups ($p > 0.05$). 40.6% (13 cases) of patients in azithromycin group and 60% (18 cases) in clindamycin group had a

Table 1: Mean of alterations in the number of cutaneous lesions in each treatment interval according to the type of therapeutic regimens.

Therapeutic regimen	Interval of first to second visit			Interval of second to third visit			Interval of third to fourth visit		
	azithromycin	clindamycin	P-value	azithromycin	clindamycin	P-value	azithromycin	clindamycin	P-value
Type of lesions									
Mean decrease in the number of papules	11.25±4.49	10.33±5.92	0.22	2.55±2.11	1.2±2.64	0.242	0.28±2.57	1.54±1.53	0.155
Mean decrease in the number of nodules	1.52±1.56	1.33±1.81	0.646	0.42±2.06	0.09±1.22*	0.156	0.25±0.75	0.75±0.88	0.015
Mean decrease in the number of pustules	0.12±1.35	0.56±0.89	0.104	0.28±1.38	0.11±0.93	0.277	-0.8±2.17	0.5±0.53	0.086

*Negative sign next to some values indicates an increase in the number of lesions

history of previous treatment for acne. These rates were not statistically significant ($P>0.05$).

Before beginning the treatment, the grade of the disease in azithromycin group was as follows: 3.1% grade 2 (1 case), 37.5% grade 3 (12 cases), 37.5% grade 4 (12 cases) and 21.9% grade 5 (7 cases). These rates in the clindamycin group were 0% grade 2 (0 case), 56.7% grade 3 (17 cases), 36.7% grade 4 (11 cases) and 6.7% grade 5 (2 cases). These rates did not show any significant difference in both groups ($P>0.05$). Also, from the beginning until the end of the study, 2 patients (6.3%) in the azithromycin group and 2 patients (6.7%) in the clindamycin group did not follow the treatment order while others did ($P>0.05$).

After a course of treatment and in the interval between the first and the second visit, in patients receiving azithromycin, 3 cases (9.4%) remained unchanged, 28 cases (87.5%) showed improvement and 1 case (3.1%) experienced deterioration of the disease; while in patients receiving clindamycin 30 cases (94.6%) showed improvement and cases with deterioration of the disease or unchanged cases were not observed (0%). Comparison of these rates by using Chi-2 test showed no significant difference ($P>0.05$). In the interval between the second and the third visit in patients receiving azithromycin, 10 cases (34.5%) had no change, 17 cases (58.6%) improved and 2 cases (6.9%) deteriorated. These rates in patients receiving clindamycin were as follows: 13 cases (43.3%) with no change, 15 cases (50%) of improvement and 2 cases (6.7%) of deterioration. Comparison of these rates did not show a significant difference, either ($P>0.05$).

In the interval between the third and the fourth visit in the patients on azithromycin, 11 patients (45.8%) had no alteration, 7 patients (29.2%) showed improvement and 6 cases (25%) became worse.

In patients on clindamycin, no alteration was seen in 12 cases (46.2 %) while 14 patients (53.8%) improved and there were no cases of deterioration (0%). Comparison of these rates by using Chi -2 test showed a significant difference ($P<0.016$).

Table 1 shows the mean of alterations in the number of papules, nodules and pustules in each treatment interval according to the therapeutic regimens.

If we consider the alterations of the disease from the beginning until the end of the therapeutic course, findings show that improvement of disease is observed in all patients receiving azithromycin and all patients receiving clindamycin. On the other hand, reduction in the number of lesions in the mentioned period from the beginning to end of the therapeutic course in patients on azithromycin and clindamycin according to the type of the lesions followed a normal distribution and mean of decrease. The number of lesions in the interval of mentioned period in the patients on azithromycin and clindamycin according to the type of lesions were as following: mean reduction in the number of papules was 13.9 ± 3.9 in azithromycin users and 13.0 ± 5.3 in clindamycin users, mean reduction in the number of nodules was 1.1 ± 1.6 in azithromycin users and 1.3 ± 0.5 in clindamycin users and mean reduction in the number of pustules was 2.0 ± 2.0 in azithromycin users and 2.1 ± 1.9 in clindamycin users. Comparison of these figures by using T test showed no statistically significant difference ($P>0.05$).

Findings show that in the interval between the first and the second visit, erythema occurred in 2 cases (6.3%) receiving azithromycin and in 2 cases (6.3%) receiving clindamycin. In the mentioned intervals, scaling occurred in 2 cases (6.3%) and 6 cases (20%) of azithromycin and clindamycin users respectively, and pruritus was observed in 0 (0%)

Table 2: Patients' satisfaction with treatment

Duration of treatment	Rate of satisfaction	Azithromycin	Clindamycin	P value
4 weeks	Very dissatisfied	0 0%	0 0%	0.168
	Dissatisfied	1 3.1%	0 0%	
	Unconfident	2 10.5%	4 10.8%	
	Satisfied	20 62.5%	24 80%	
	Very satisfied	8 25%	2 6.7%	
	Total	32 100%	30 100%	
8 weeks	Very dissatisfied	0 0%	0 0%	0.256
	Dissatisfied	2 6.8%	2 6.7%	
	Unconfident	1 3.4%	4 13.3%	
	Satisfied	13 44.9%	18 60%	
	Very satisfied	13 44.9%	6 20%	
	Total	29 100%	30 100%	
12 weeks	Very dissatisfied	0 0%	0 0%	0.328
	Dissatisfied	1 3.4%	0 0%	
	Unconfident	1 3.4%	0 0%	
	Satisfied	18 62.1%	22 78.6%	
	Very satisfied	9 31%	6 21.4%	
	Total	29 100%	28 100%	

Table 3: Side effects due to topical azithromycin or clindamycin in the treatment of acne according to sex of patients

Side effects	erythema						scaling						pruritus					
	4		8		12		4		8		12		4		8		12	
Sex	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Therapeutic regimens																		
Azithromycin	0 0%	2 18.2%	1 5%	1 10%	1 5%	3 30%	1 4.8%	1 9.1%	0 0%	0 0%	2 10%	3 30%	0 0%	0 0%	3 15%	0 0%	1 5%	3 30%
Clindamycin	2 9.1%	0 0%	0 0%	0 0%	0 0%	0 0%	6 27%	0 0%	0 0%	0 0%	0 0%	0 0%	2 9.1%	2 25%	0 0%	0 0%	0 0%	0 0%
p-value	0.157	0.202	0.288	0.357	0.476	0.090	0.046	0.579	-	-	0.129	0.090	0.157	0.080	0.059	-	0.282	0.090

azithromycin users and 4 (13.3%) clindamycin users. Comparison of the mentioned figures by using Chi-2 test show that incidence of erythema in the two groups did not show a statistically significant difference ($P>0.05$), while for scaling, it was close to the significant level ($P=0.107$) and the difference for pruritus was significant ($P=0.033$). In the interval between the second and the third visit, erythema occurred in 2 cases (6.9 %) out of 29 azithromycin users but in none (0%) of the 30

clindamycin users. Scaling, as a side effect, occurred in none (0 %) of the 29 azithromycin users and 30 clindamycin users while pruritus was observed in 3 (10.3 %) of the 29 azithromycin users and 1 (2.7 %) of the 30 clindamycin users. Comparison of the mentioned figures using Fisher exact test showed no statistically significant difference ($P>0.05$) (for pruritus it was close to the significant level, $P=0.081$).

In the interval between the third and the fourth visit, erythema was observed in 4 (13.7%) of the 29 cases receiving azithromycin but in none of the 28 cases (0%) receiving clindamycin. Comparison of these figures showed a significant difference close to the significant level ($P=0.083$). In the mentioned interval, 5 patients out of 29 cases (17.2%) who received azithromycin and none of the 28 cases (0%) who received clindamycin suffered from scaling as a side effect. Comparison of these figures showed a significant difference, as well ($P=0.02$). Our findings showed that 4 cases out of 29 cases (13.7%) receiving azithromycin and none of the 28 cases (0%) receiving clindamycin suffered from pruritus. Comparison of these figures showed a significant difference ($P=0.038$).

Table 2 shows the rate of patients, satisfaction according to the type of therapeutic regimens as well as P -values.

Results of this study showed that in female patients who received azithromycin, the rate of improvement in the interval between the first and the second visit was 95.2% (21 from 22) while it was 100% (22 cases) in those who used clindamycin; however, these rates were not significantly different ($P>0.05$). In male patients who used azithromycin, the rate of improvement was 80% (8 from 10 cases) in the interval between the first and the second visit while it was 100% (8 cases) in those who used clindamycin. Comparison of these figures did not show a significant difference ($P=0.107$).

In female patients who used azithromycin, the rate of improvement was 57.9% (11 from 19 cases) in the interval between the second and the third visit, but in those who used clindamycin, 59.1% (13 out of 22 cases) showed improvement. Comparison of these figures was not significantly different ($P>0.05$). In male patients who were on topical azithromycin, the rate of improvement was 70% (7 from 10) in the interval between the second and the third visit; but in those who used clindamycin, 25% (2 from 8 cases) showed improvement. Comparison of these figures showed a difference close to the significant level ($P=0.06$).

In the interval between the third and the fourth visit, the rate of improvement in female patients who used azithromycin and clindamycin was 20% (3 from 15) and 60% (12 from 20), respectively. Comparison of these figures showed a significant difference ($P=0.007$). In male patients who used azithromycin and clindamycin, the rate of improvement was 44.4% (4 from 9) and 33.3% (2 from 6), respectively, which was not significant

($P>0.05$). The rate of improvement in the interval between the first and the fourth visit in both sex groups and both treatment groups was 100%.

Table 3 shows rates of side effects due to applying each drug separately based on sex and time of occurrence of side effects. Comparison of these rates does not show a significant difference.

Findings show that the alteration mean in the grade of the disease at the end of therapeutic course in comparison with the beginning of the treatment in female azithromycin users was 2.63 ± 1.11 with a median of 3. These data in female clindamycin users was 2.86 ± 0.94 with a median of 3. Comparison of these data using Wilcoxon test did not show a significant difference ($P>0.05$). Mean of alterations in the grade of the disease at the end of the therapeutic course in comparison with the beginning of the treatment in male azithromycin users was 2.9 ± 0.87 with a median of 3. These data in male clindamycin users was 2.5 ± 0.53 with a median of 3. Comparison of these data using Wilcoxon test did not show a significant difference ($P>0.05$).

Discussion

At present, there is an agreement among dermatologists on using one topical retinoid and a topical antibiotic both together for the treatment of mild acne¹⁵⁻¹⁷, but vast using of clindamycin and erythromycin have resulted in increasing the rates of resistance to these two topical antibiotics¹⁸, therefore, the need for some new topical antibiotics such as azithromycin is felt. Azithromycin, as a member of macrolides family, is effective against a vast spectrum of gram positive and gram negative bacteria as well as anaerobes and its effectiveness has been shown on the causative microorganisms in acne¹⁹.

Results of our study showed that topical azithromycin is as effective for the treatment of mild acne as topical clindamycin. These results showed that the peak of therapeutic effect was achieved in the first month of therapy in both groups which would result in increasing the compliance for using drugs by the patients, psychologically. Therapeutic effects of both antibiotics were observed up to the end of the treatment course with a few differences on all types of coetaneous lesions. Our study showed that the rates of side effects in both groups are little and negligible. Although scaling occurred more in the first month of treatment in patients treated with clindamycin, more side effects were noticed in the patients receiving azithromycin. Although these

results need more evaluation, it seems that having bigger molecules in azithromycin and more absorption in inflammatory areas result in more side effects in this antibiotic.

In spite of small differences in the side effects of the drugs, the rate of patients, satisfaction with their treatment was high (very high in the majority of cases in both therapeutic regimens) and therefore, there was no difference between these two prescribed regimens.

Our study showed that there was no difference between the two regimens in men and women in the first and second months of treatment but female patients showed a better therapeutic response to clindamycin during the last months of treatment. There was no difference in the duration of treatment between two drug regimens in male patients.

Our findings state that there is a significant and reverse association between the age of the patients and some types of the lesions; in other words, the older the patients are, the less pustules respond to treatment. This fact was observed in both azithromycin and clindamycin groups.

In conclusion, findings of this study show that since resistance to azithromycin has not been reported in the recent studies²⁰, azithromycin might be considered as a new effective drug for mild acne. Of course performing more studies in this field is necessary to address some unanswered questions and unexplained findings.

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References

1. Mc Hugh RC, Rice A, Sangha ND, et al. A topical azithromycin preparation for the treatment of acne vulgaris and rosacea. *J Dermatolog Treat* 2004;15:295-302.
2. Ozolins M, Eady EA, Avery AT, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomized controlled trial. *Lancet* 2004;364:2188-95.
3. Zhang JZ, Li LF, TuYT, et al. A successful maintenance approach in inflammatory acne with adapalene 0.1% after an initial treatment in combination with Clindamycin topical solution 1% or after monotherapy with Clindamycin topical solution 1%. *J Dermatolog Treat* 2004;15:372-8.
4. Ozolins M, Eady EA, Avery A, et al. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. *Health Technol Assess* 2005;9: 212.
5. Krautheim A, Gollnick HPM. Acne: Topical treatment. *Clin Dermatol* 2004;22: 398-407.
6. Tan J. Update on topical acne treatment. *Skin Therapy* 1999;5:47.
7. Bershad SV. The modern age of acne therapy: a review of current treatment options. *Mt Sinai J Med* 2001;68:279-86.
8. Loveckova Y, Havlikova I. A microbiological approach to acne vulgaris. *Biomed Papers* 2002;146:29-32.
9. Kapadia N, Talib A. Acne treated successfully with azithromycin. *Int J Dermatol* 2004;43:666-67.
10. Fernandez- Obregon AC. Azithromycin for the treatment of acne. *Int J Dermatol* 2000;39:45-50.
11. Kunyetz R. Systemic antibiotic therapy for acne: a review. *Skin Therapy Lett* 2002;7:3-7.
12. Leyden JJ. Effect of topical benzoyl peroxide / clindamycin versus topical clindamycin and vehicle in the reduction of propionibacterium acne. *Cutis* 2002; 69:475-6.
13. Katsambas AD, Stenfanaki C, Cunliffe WJ. Guidelines for treating acne. *Clin Dermatol* 2004;22:439-44.
14. O'Brien SC, Lew's JB, Cunliffe WJ. The Leeds revised acne grading system. *J Dermatolog Treat* 1998;9:215-20.
15. Gollnick HA, Cunliffe WJ. Management of acne: A report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol* 2003;1:1-37.
16. Wolf JE, Kaplan D, Kraus S, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blind study. *J Am Acad Dermatol* 2003;49(suppl.3):S227-32.
17. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris. *J Am Acad Dermatol* 1997; 36:26-34.
18. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic resistant acne: Lessons from Europe. *Br J Dermatol* 2003; 148: 467- 78
19. Wolverton SE(ed). *Comprehensive dermatologic drug therapy*. Indianapolis: Saunders; 2007.
20. Ruggero C, Mauro B, Stefano V. Pulse therapy with azithromycin: an open study. *J Am Acad Dermatol* 2004;50:11.