

A Comparative Study of Azithromycin Versus Doxycycline in the Treatment of Acne Vulgaris

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Abstract

Introduction: Acne vulgaris is seen in nearly 100% of individuals at some time during their lives. Treatment is essential to prevent physical and psychological 'scarring'. Systemic treatments such as Azithromycin and Doxycycline are used in routine clinical practice worldwide.

Objectives: To compare the efficacy of Azithromycin and Doxycycline in the treatment of acne vulgaris

Methods: Sixty six patients with acne vulgaris fulfilling the selection criteria, visiting the out patients department of Dhulikhel Hospital, Kathmandu University Teaching Hospital, between December 2009 to June 2010, were selected for this open prospective study. They were assigned to two treatment groups; first group received oral pulse therapy of Azithromycin and the second group oral Doxycycline daily, for a period of three months.

Results: Overall zero grades were achieved by 22/35 (62.9%) of patients in Azithromycin group and 23/31 (74.2%) of patients in Doxycycline group. However, no statistically significant difference in the effectiveness of the two drugs was seen. Doxycycline was found to be less expensive than Azithromycin. More (statistically significant) side effects were observed with Doxycycline than Azithromycin.

Conclusion: Both drugs were effective in reducing the severity of acne vulgaris. The comparative efficacies of the drugs were not statistically significant. Azithromycin was shown to have fewer side effects and its compliance is better due to ease of administration (pulse dose). However, as both drugs have similar efficacy, Doxycycline can be used as an alternative drug or for patients in whom cost is a problem as it is less expensive than Azithromycin.

Key words: Acne vulgaris, Azithromycin, Body dysmorphic disorder, Doxycycline

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Introduction

Since ancient times, physical attractiveness has been socially advantageous and has been associated with the perceptions of goodness, success and a sense of well-being. Dysmorphic dermatoses such as acne vulgaris, hyperpigmentation and hypopigmentation, signs of aging and scarring have a significant impact on patient's quality of life namely: relationship to others, self-image, self-esteem and economic opportunities.^{1,2} Hence, there is an increased demand for aesthetic information and treatments, not only for patients suffering from body dysmorphic disorders but also for those who want their appearance to match their inward perception of youth and vitality.

Acne vulgaris is a chronic inflammatory disorder of pilosebaceous unit which frequently affects the cosmetically important areas of the body like face, back, chest, neck and upper arms. It is a multifactorial disease and its pathophysiology centers on the interplay of increased sebum production, follicular hyperkeratinization, colonization with *Propionibacterium acnes* and inflammation.³ Acne represents a spectrum of disease with severity ranging from a couple of blackheads to fulminant acne. The severity of the disease differs from patient to patient and treatment must be tailored accordingly, with the goal of preventing physical and/or psychological 'scarring'.

There are many topical and systemic modalities for acne treatment.⁴ *P. acnes* is highly sensitive in vitro to a number of antimicrobial agents of different classes, including Macrolides, Tetracyclines, Penicillins, Clindamycin, Aminoglycosides, Cephalosporins, Trimethoprim, and Sulfonamides.³ The efficacy of these agents depends on their ability to reach the lipid-rich environment of the pilosebaceous follicles where *P. acnes* proliferate. Thus, the choices of systemic antibiotic agents for treating acne include Tetracycline, Doxycycline, Minocycline, Erythromycin, Trimethoprim, and Azithromycin. Systemic treatments such as Azithromycin and

Doxycycline are used routinely in clinical practice worldwide.⁵

The antibacterial effect of Azithromycin, like that of other macrolide antimicrobials, has been attributed to reversible binding to the 50S ribosomal subunit within the bacterial cell, with consequent inhibition of protein synthesis.³ Through this mechanism, Azithromycin exerts bacteriostatic, and sometimes bactericidal effects. It is not known if the antimicrobial activity of Azithromycin against nonbacterial species is attributed the same mechanism of action. Doxycycline inhibits bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit and preventing the association of aminoacyl-tRNA with the bacterial ribosome.³ Further inhibition of protein synthesis occurs in mitochondria through binding to the 70S ribosomes. It is therefore a bacteriostatic drug. Effective management has become increasingly challenging with the emergence of antibiotic-resistant strains of *P. acnes*.⁶ Till date, data about the medication used to treat acne vulgaris in Nepal could not be found. In practice, however, oral antibiotics have been used in treating acne vulgaris since long. There is neither any document validating the efficacy of these drugs nor any paper comparing the efficacy of these drugs, published from Nepal.

This comparative study was conducted to find out which among Azithromycin and Doxycycline is more efficacious, cost effective and has fewer side effects in the treatment of acne. Results of this study would be useful in making recommendation in relation to the overall therapeutic management of acne vulgaris.

Materials and Methods

This was an open prospective study. Patients with acne vulgaris, visiting the out patients department of Dhulikhel Hospital, Kathmandu University Teaching Hospital, between December 2009 to June 2010, were selected for the study. Patients of 15 to 35 years of age of any gender were included.

Original Article*Exclusion criteria*

- i. Pregnant or lactating women.
- ii. Topical treatment in last 2 weeks before the study.
- iii. Use of systemic antibiotic in the last 3 weeks before the study.
- iv. Using hormonal contraceptives.
- v. Refuse to consent or factors that limited the capacity of cooperation.
- vi. Patients with chronic underlying diseases/conditions.
- vii. Known hypersensitivity to the study drug.

A set of questionnaire was prepared and a pilot study was done for 10 patients for possible modification for better understanding and convenience to the subjects. As per requirement, modification was done in the questionnaire and these 10 patients were also included in the study. Patients who fulfilled the selection criteria were informed in detail about the study being done and about their contribution in the study. In case if patients were not able to answer or were physically or mentally disable, informed consent was taken from the patient party. After taking written consent, the parameters including age, sex, duration of lesion, site of lesion, grade, relation to menstrual cycle, etc as per questionnaire were obtained.

Acne vulgaris was graded using a simple grading system taking into account the predominant lesion to grade acne, which classifies the acne vulgaris into four grades⁷:

Grade I: Comedones, occasional papules.

Grade II: Papules, comedones, few pustules.

Grade III: Predominant pustules, nodules, abscesses.

Grade IV: Mainly cysts, abscesses, widespread scarring.

Grade Zero: This was used at the end of treatment and during the follow-up and defined as nonexistence of the lesions.

The sixty six (66) patients who fulfilled the selection criteria were assigned to two treatment groups: Group A: included thirty-five (35) patients who were given Azithromycin pulse therapy (500 mg/day for 3 consecutive days a week for 12 weeks). Group B: included thirty-one (31) patients who were given Doxycycline 100 mg/day for the three months.

In both the groups, the patients were provided with the medication from the same pharmaceutical company (NPL-Nepal Pharmaceutical Laboratory, Bara, Nepal) namely: AZITH[®] 500 (Azithromycin 500mg Tablet) and DOXYN[®] 100 (Doxycycline 100mg Capsule).

The data collected were compiled and processed using Microsoft Excel Worksheet. Statistical analysis was carried out by using Statistical Package of Social Sciences (SPSS) version 11.5. Data were represented in the form of mean plus minus standard deviation (SD), where applicable. A *p-value* less than 0.05 were considered to be statistically significant.

RESULTS

Table 1.1 Demographic characteristics of the study population

Variables	Characteristics	Azithromycin (n=35)		Doxycycline (n=31)		Total (%)		p-value
		No.	%	No.	%	No.	%	
Age (Year)	Mean± SD	22.1±3.8		20.1±3.4		21.2±3.7		0.381
Age Groups (Year)	<20	14	40.0	18	58.1	32	48.5	
	20-24	14	40.0	10	32.3	24	36.4	
	25-29	4	11.4	3	9.7	7	10.6	
	30-35	3	8.6	0	0.0	3	4.5	
Gender	Male	12	34.3	14	45.2	26	39.4	0.257
	Female	23	65.7	17	54.8	40	60.6	
	Student	25	71.4	26	83.9	51	77.3	0.371
Occupation	Housewives	4	11.4	1	3.2	5	7.6	
	Service	6	17.1	4	12.9	10	15.2	
	Brahmin	14	40.0	8	25.8	22	33.3	0.018
Ethnicity	Newar	10	28.6	14	45.2	24	36.4	
	Chhetri	4	11.4	4	12.9	8	12.1	
	Gurung	1	2.9	1	3.2	2	3.0	
	Others §	6	17.1	4	13.0	10	15.1	

§: Karki, Tamang, Lama, Shah

Table 2.1 Severity of acne after first, second and third months of treatments in Azithromycin and Doxycycline group

Score	Azithromycin (n=35)				Doxycycline (n=31)			
	Baseline	After 1 month treatment	After 2 month treatment	After 3 month treatment	Baseline	After 1 month treatment	After 2 month treatment	After 3 month treatment
0	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
1	NA		10(28.6)	22 (62.9)	NA	1(3.2)	12(38.7)	23(74.2)
2	2(5.7)	8(22.9)	16(45.7)	9 (25.7)	3(9.7)	14(45.2)	16(51.6)	7(22.6)
3	10(28.6)	22(62.9)	8(22.9)	3(8.6)	19(61.3)	15(48.4)	3(9.7)	1(3.2)
4	19(54.3)	4(11.4)	0(0.0)	0(0.0)	7(22.6)	1(3.2)	0(0.0)	0(0.0)
	4(11.4)	1(2.9)	1(2.9)	1(2.9)	2(6.5)	0.0(0.0)	0(0.0)	0(0.0)

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Table 2.2 Comparative efficacy of Azithromycin and Doxycycline with p-values

Variables	p-value
After 1 month treatment of Azithromycin and After 1 month treatment of doxycycline	0.162
After 2 month treatment of Azithromycin and After 2 month treatment of doxycycline	0.358
After 3 month treatment of Azithromycin and After 3 month treatment of doxycycline	0.056

Table 2.3 Individual efficacies of Azithromycin and Doxycycline

Duration of treatment	Treatment to the patients	
	Azithromycin	Doxycycline
	p-value	p-value
Baseline to first month treatment	0.015	0.0045
First month treatment to second month treatment	0.0001	0.00035
Second month treatment to third month treatment	0.033	0.018

Table 3.1 Side effects of the study drugs

Side effects	Treatment to the patients				Total		p-value
	Azithromycin		Doxycycline		No	%	
	No.	%	No.	%	No	%	0.044
None	28	80.0	24	77.4	52	78.8	
Super infection	0	0.0	1	3.2	1	1.5	
Nausea and vomiting	3	8.6	1	3.2	4	6.1	
Photosensitivity	0	0.0	3	9.7	3	4.5	
Headache	0	0.0	2	6.5	2	3.0	
Abdominal pain	4	11.5	0	0.0	4	5.8	
Diarrhea	2	5.7	0	0.0	2	3.0	

Table 4.1 Cost comparison of Azithromycin and Doxycycline

Description (per patient)	AZITH 500*	DOXYN *
Average dose	1500mg/ week	100mg/ day
Cost (Rupees)	30.0/500 mg	4.0/100 mg
Cost per month	360.00	120.00
Cost per three month	1080.00	360.00

*Brand name of NPL (AZITH 500- Azithromycin 500mg Tablet, DOXYN-Doxycycline 100mg Capsule)

The mean age of acne vulgaris patient was 22.1 ± 3.8 for Azithromycin group and 20.1 ± 3.4 for Doxycycline group, respectively. There was no significant difference in age (*p*-value 0.381) of the patient taking Azithromycin group and Doxycycline group.

Gender was equally distributed (*p*-value 0.257) in both groups. Number-wise however, there were more female patients than males, in both the groups.

A majority of the patients were students (77.3%), followed by service holder (15.2%) and housewife (7.6%). However, this was not statically significant (*p*= 0.371).

Among the total study population, most of the patients were Newar (36.4%), followed by Brahmin (33.3%). In our study, Newar community predominates in having acne vulgaris, because the study was conducted in the hospital situated amidst Newar community.

Tables 2.1, 2.2, and 2.3 show the overall efficacy of acne treatment with Azithromycin and Doxycycline.

The comparative efficacy of Azithromycin and Doxycycline group patients is shown in table 2.1. After 3 months of treatment, in Azithromycin group, 62.9% of patients were in Grade Zero, 25.7% in Grade I, 8.6% in Grade II, 0% in Grade III and 2.9% in Grade IV. Whereas, in Doxy group, 74.2% of patients were in Grade Zero, 22.6% in Grade I, 3.2% in Grade II, 0% in Grade III and 0% in Grade IV.

Table 2.2 shows the difference in response between the two groups during first, second and third months of treatment. The values were not statistically significant implying that there was no difference in the effectiveness of Azithromycin and Doxycycline during the treatment period. The severity of acne grading was found to be reduced during the first, second and third months of treatments (table 2.3). The difference in response during these months were found to be

statistically significant (*p* < 0.05) indicating that both drugs were effective in reducing the severity of acne grading.

The detailed side effect profile of both drugs is given in Table 3.1. Abdominal pain (11.5%), nausea and vomiting (8.6%), and diarrhea (5.7%) were the major side effects experienced by the patients on Azith group whereas photosensitivity (9.7%), headache (6.5%), superinfection (3.2%) and nausea and vomiting (3.2) were major side effects in Doxy group.

Overall, patients in Doxycycline group experienced more (22.6%) side effects compared with patients in (20%) in Azithromycin group. However, no additional medication was required to relieve side effects in either group. Drug cost of unit dose for Doxycycline was found to be less than that of Azithromycin. The cost of treatment with Doxycycline was also found to be less than that of Azithromycin. The total cost for individual patient up to three months of treatment was Rs. 360/- NPR for Doxycycline and Rs. 1080/- NPR for Azithromycin. The cost comparison would be helpful in recommending the affordable one between two therapeutically equivalent drugs. Doxycycline was found to be therapeutically equivalent and cheaper than Azithromycin.

Discussion

In this study, most of the patients (48.5%) belonged to the age group of less than 20 years followed by that of 20-24 years age group. An analysis of the 1996 census data in the United States of America indicated that the prevalence of acne in the age group 12 -24 was more (85%).⁸ A similar result has been obtained in our study. According to study by Cunliffe WJ, Gould DJ, after an age of somewhere between 20 and 25 years, acne resolves slowly.⁹

Female patients were found to be more in both the groups, in our study. This is in congruence with the study by Kilkenny M, Merlin K, Plunkett A, Marks R on school students in Victoria which found that 97.8% of boys and 89.8% of girls aged

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16-18 suffered with acne.¹⁰ According to Burton et al, acne develops earlier in females than in males.¹¹ The onset of clinical acne in girls than boys is presumably related to their earlier puberty. Some subjects show small non-inflamed lesions by the age of 8-9 years.

In our study, the highest prevalence rate was among student population. This is in conjugation with the research and explanation by Kilkenny et al and White GM.^{10,12} The research by Kilkenny et al on school students in Victoria was further justified by White GM who suggested that the higher teenage prevalence of acne was possibly related with pubertal changes and to a lesser extent with stress, cosmetics use etc.

A randomized, investigator-blinded study was performed by Kus S, Yucelten D, Aytug A to compare the efficacy of Azithromycin with Doxycycline.¹³ Fifty-one patients were randomized to receive either Azithromycin 500 mg/day on three consecutive days per week in the first, two consecutive days per week in the second, and one day per week in the third month. The other group was given Doxycycline twice a day for the first month and once a day for the second and third months. Statistically significant improvement in the facial acne lesions with Azithromycin and Doxycycline was found in the study. However, neither drug was shown to be more effective than the other.

A study conducted by Singhi MK, Ghiya BC, Dhabhal RK, suggests that the combination of Azithromycin with topical Erythromycin was significantly better than the combination of Doxycycline with topical Erythromycin in the treatment of acne vulgaris.¹⁴ This non-randomized controlled trial was conducted on 70 outpatients with acne vulgaris. In the first group, Azithromycin was administered 500 mg daily before meals for 3 consecutive days in a 10-day cycle, with remaining 7 days in the cycle being drug-free days. The second group was given Doxy 100 mg daily after meals. There was 77.26% improvement in Azithromycin treated group in comparison to 63.74% in the Doxy treated group.

In our study, both Azithromycin and Doxycycline were found to be effective in the treatment for acne. This is in congruence with the aforementioned studies by Kus S, Yucelten D, Aytug A and Singhi MK, Ghiya BC, Dhabhal RK.^{13,14} There was a slightly higher percentage of improvement in the Azithromycin group in the study performed by Singhi MK, Ghiya BC, Dhabhal RK.¹⁴ However, this difference could be due to the inter-subject and intra-subject variation among the study population. Kus S, Yucelten D, Aytug A reported fewer side effects compared with our study which might be due to the lesser no of subjects (n=45) in the study.¹³ In their study, Singhi MK, Ghiya BC, Dhabhal RK reported following side effects: three patients with diarrhea, four with gastric upset, one with esophageal ulceration and one with photo-onycholysis, in the Doxycycline treated group and gastric upset among three patients in Azithromycin treated group.¹⁴ We did not encounter esophageal ulceration and photoonycholysis in our study but we did come across a few cases of dyspepsia in both the treatment groups and photosensitivity in three patients in the Doxy treated group. More (statistically significant) side effects were observed with Doxycycline than Azithromycin. No patient had to drop out from the study due to side effects. When this study was initiated, not a single study regarding epidemiology of acne, its prevalence or anti-acne drugs used in Nepal could be found during literature search. So, comparison of our study with another study conducted in Nepal could not be done.

Though our study was limited by a small number of subjects and its short duration, we believe that the findings of this study will help dermatologist and physicians in clinical practice. The study also calls for further studies regarding acne vulgaris and its management in the context of Nepal, in a wider scale.

Conclusion

Both Azithromycin and Doxycycline are effective in reducing the severity and progression of acne vulgaris. The cost of treatment with Doxy was

found to be less than that of Azithromycin. The number of side effects observed with Azithromycin is lesser (statistically significant) than that of Doxycycline.

With evidence regarding efficacy, side effects and ease of administration (pulse dose vs. once daily) treatment of acne vulgaris with systemic therapy using Azithromycin is preferable than Doxycycline. However, when it is well tolerated, Doxycycline is very cost effective drug and as efficacy of both drugs is similar, Doxycycline can be used as a good alternative to Azithromycin

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