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RESEARCH ARTICLE

A comparison of cost-effectiveness between doxycycline and azithromycin with topical clindamycin in the treatment of patients with moderate to severe acne vulgaris: Prospective, randomized study

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ABSTRACT

Background: Acne vulgaris is one of the chronic, common dermatological skin diseases with inflammatory lesions, prevalent among adolescents. The management of acne vulgaris is primarily pharmacotherapy comprising both topical and systemic anti-inflammatory and antimicrobials agents. **Aims and Objective:** Pharmacoeconomic analysis is now an integral part of therapy. There are several studies regarding recommendations, guidelines, efficacy, tolerability, and outcomes of therapies used in acne vulgaris; but hardly any studies comparing the cost-effectiveness of this combination of topical and oral antimicrobials in the treatment of moderate to severe acne vulgaris in our country; hence, this study was taken up to provide useful and valid data. **Materials and Methods:** This was a randomized, open-label, active-controlled, comparative study of cost-effectiveness analysis of doxycycline and azithromycin in 60 subjects, who gave written informed consent and had moderate to severe acne vulgaris. Azithromycin was given as pulse therapy whereas doxycycline was given once daily with topical clindamycin twice daily for 8 weeks in both groups. Direct and indirect medical costs were considered, average cost-effectiveness ratio (ACER) and cost-effective analysis (CEA) were analyzed. Non-parametric test like Mann–Whitney test was used to access the efficacy of the drugs and the result was statistically significant. Results were depicted in the form of tables, figures, and graphs. **Results:** The ACER and CEA showed that azithromycin was better than doxycycline. **Conclusion:** The study drugs were effective in reducing the lesion count but required long-term treatment; however, azithromycin was more cost-effective than doxycycline.

KEY WORDS: Acne Vulgaris; Azithromycin; Cost-effective Analysis; Doxycycline

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles characterized by comedones, papules, pustules, nodules, and often scars.[1] It can affect any age group but most prevalent among adolescents and young adults.[2] The pathogenesis is multifactorial, which includes androgen-mediated stimulation of sebaceous gland activity, abnormal keratinization leading to follicular plugging (comedone formation), inflammation of the follicle, and surrounding dermis due to *Propionibacterium* acnes. It can cause physical, psychological morbidity due to poor self-image and scarring as it affects primarily the face, neck, upper trunk, and upper arms. Acne typically develops around puberty that is around 8–12 years due to increased sex hormone production and is frequently comedonal in character initially and later becomes inflammatory pustules, nodules, and scars. Acne can also

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occur in older age sometimes around the sixth decade of life. Males with oily skin and in females who use cosmetics and before menstruation, acne is more prevalent.

Acne vulgaris can be graded into four types based on the global acne grading scale:[3] Grade 1 (mild): Comedones and occasional papules, which are treated with topical pharmacotherapy such as benzyl peroxide, azelaic acid, adapalene, retinoids, and clindamycin.[4,5] Grade 2 (moderate): Comedones, papules, and few pustules; Grade 3 (severe): Pustules, nodules, and abscesses; Grade 2 and Grade 3 are treated with topical and oral antimicrobials such as macrolides erythromycin, azithromycin, tetracyclines-doxycycline, minocycline, and occasionally isotretinoin.[6,7] Grade 4 (cystic): Mainly cysts/abscesses and widespread scarring are treated with topical tretinoin, isotretinoin, oral contraceptives, corticosteroids, and comedone extraction, laser and surgery. Ade 1 (mild): Comedones and occasional papules, which are treated with topical pharmacotherapy such as benzyl peroxide, azelaic acid, adapalene, retinoids, and clindamycin are the treatment of choice.[4,5] Grade 2 (moderate): Comedones, papules, and few pustules; Grade 3 (severe): Pustules, nodules, and abscesses; Grade 2 and Grade 3 are treated with topical and oral antimicrobials such as macrolides erythromycin, azithromycin, tetracyclines-doxycycline, minocycline, and occasionally isotretinoin are the treatment of choice.[6,7] Grade 4 (cystic): Mainly cysts/abscesses and widespread scarring are treated with topical tretinoin, isotretinoin, oral contraceptives, corticosteroids, and comedone extraction, laser and surgery are available treatment options.[8]

Doxycycline is a broad-spectrum tetracycline, being lipophilic in nature, it can easing penetrate follicles infected with *Propionibacterium* acne and decrease sebum production; effective in treating inflammatory acne has convenient dosage schedule, without any serious adverse effects except photosensitivity, oesophagitis is seen.[9] Azithromycin is a macrolide antibiotic, safe and is effective in decreasing sebum production, can be given in pulse therapy with minimal gastrointestinal side effects, and has good patient compliance.[10] Clindamycin is used in the topical form in the treatment of acne, works by suppressing the growth of *Propionibacterium* acne and reducing inflammation.[11] Doxycycline and azithromycin both help in reducing acne lesion count and azithromycin have special advantage of being less expensive with fewer side effects and better compliance due to pulse regimen[12,13]; in this study, oral and topical antimicrobials are used in combination to decrease resistance and faster reduction in acne lesion count.

Pharmacoeconomic is gaining importance in every aspect of health care, as it is the analysis of the cost of drug therapy to health-care systems and society and compares the costs and outcomes of the alternatives considered. It not only includes clinical and economic consequences but also outcomes such as patient's health status and satisfaction with health care. In acne vulgaris early and effective treatment of lesions are vital to prevent facial scars that lead to the cosmetic and psychological impact on the subjects. It also causes an economic burden to the patient and the family due to the cost of the medication used for lesion clearance.

In spite of the availability of various therapies, standard guidelines, and recommendations, the outcome of these therapies is still unsatisfactory with regard to efficacy, tolerability, safety and adverse effects, and costs. Currently, there are few studies in Indian population available on comparison of cost-effectiveness in acne vulgaris and hardly any study comparing cost-effectiveness between these groups of drugs, doxycycline and azithromycin with topical clindamycin in the treatment of moderate to severe acne vulgaris. This study was taken up to highlight how the cost and clinical outcome can affect the treatment of acne vulgaris.

MATERIALS AND METHODS

Trial Design

This study was designed as a randomized, open-label, parallel-group study of the cost-effectiveness of doxycycline and azithromycin in moderate to severe acne vulgaris. The study was registered prospectively with Clinical Trial Registry, India (CTRI/2018/12/016711).

Materials and Place of Study

The study was conducted in the Department of Dermatology, Kempegowda Institute of Medical Sciences and Research Center, Bengaluru between November 2018 and January 2019. The study included 60 subjects who were having moderate to severe acne vulgaris, randomized into two groups – azithromycin and doxycycline in 1:1 ratio using the randomization table.

The subjects included in the study were of both sexes of age group 18-35 years. Subjects who were willing to give written informed consent and available for regular follow up. Subjects who had moderate to severe acne vulgaris as per the global acne grading scale. Subjects who were ready to stop using all other acne medications during study. Female subjects of who were not pregnant and breastfeeding.

The subjects were excluded from the study if they had any serious life threatening medical condition. Subjects with severe acne, nodulocystic lesions, acne fulminans or any other type of acne or Secondary acne (drug induced). Subjects using other anti-acne medications in the past month before study entry. Subjects with history of allergy to study medications.

Methodology

Approval was taken from Institutional Ethics Committee (KIMS/IEC/A41-2018) before the commencement of the study, 60 subjects who met the inclusion and exclusion criteria were included in the study. A voluntary written informed consent was obtained from all the study subjects and or/their legal representatives before their enrolment into the study, after explaining the study details to their satisfaction. This study was conducted according to latest ICH and GCP guidelines.

The subjects were assigned either to the azithromycin and clindamycin group (n = 30) and the doxycycline and clindamycin group (n = 30) based on the randomization table. The baseline features such as demographic details, duration of previous illness, history of acne or any systemic disease, family history, history of antibiotic or any other medication usage for acne, history of any regular medication, facial comedone and inflammatory lesion count, presenting complaints, and systemic examination findings were recorded in specially designed case record form. Each subject underwent local and systemic examination during subsequent visits (2 weeks, 4 weeks, 6 weeks, and 8 weeks). Both the groups were advised to take the medications in the form of tablets (p.o) with plenty of water. Group A – 30 subjects received tab doxycycline 100 mg once a day after a meal for 8 weeks. Clindamycin gel 1% was advised to be applied on the skin twice a day for 8 weeks. Female subjects on doxycycline were asked to undergo urine pregnancy tests during baseline and counseled against conceiving when on treatment. Group B – 30 subjects received tab azithromycin 500 mg once a day for 3 times a week (pulse therapy) after a meal for 8 weeks. Clindamycin gel 1% was advised to be applied on the skin twice a day for 8 weeks.

Efficacy was measured in terms of reduction of facial comedone count and inflammatory lesion count[14,15] from baseline to follow-up weeks (2 weeks, 4 weeks, 6 weeks, and 8 weeks). Adverse effect if any was also noted. Cost-effective analysis (CEA) was carried out using the following cost measurements.[5,14] Direct medical costs included study medication costs, outpatient visit cost, and investigation cost. Direct non-medical costs included transportation expenditure for both subjects and their attendee was calculated using local public bus transport (BMTC) fares for the year 2018 (Rs. 3/km). The traveling expenditure was calculated for one-time journey (onward and outward journey).

Indirect medical costs such as loss of wages were calculated by obtaining the subjects' monthly income. Loss of leisure time and loss of wages of subjects' caretaker/s (attendee/s) were standardized as per minimum wage rate and variable dearness allowance by Ministry of Labor and Employment, Government of India, 2018. (Rs. 516/day in Bengaluru for semi-skilled, Rs. 471/day unskilled workers, and Rs. 565/day for skilled workers).

Units Costs

Cost of the study medications

Medications of the same brand were used for the entire duration of the study. The cost of all study medications was calculated based on the retail selling price of hospital pharmacy. All direct medical costs are mentioned in Table 1.

The CEA[5] was analyzed using two tools average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER). Medical costs were measured using monetary terms and clinical outcome in terms of symptom-free days (acne clear skin). Adverse events if any and cost incurred in the management were considered for CEA analysis.

The CEA was analyzed using ACER and ICER for both patients' perspectives.

ACER was calculated using the formula:

$$\text{ACER} = \frac{\text{Total cost of the drug}}{\text{Effectiveness of the drug}}$$

The symptom-free days (acne clear skin) was considered as a measure of the effectiveness of the study drugs.

ICER was calculated using the formula:

$$\text{ICER} = \frac{\text{Total costs of doxycycline-Total costs of azithromycin}}{\text{Effectiveness of doxycycline-Effectiveness of azithromycin}}$$

Table 1: Direct medical costs of azithromycin and doxycycline groups[5]

Direct cost parameters	Unit costs (INR)	Total costs (INR)	Total cost (INR)
		Azithromycin (n=30)	Doxycycline (n=30)
OPD charges	20 per visit	100 (four follow-up)	100 (four follow-up)
UPT charges	120 per patient	-	1440 (for 12 patients)
Tab azithromycin 500 mg	20 per tab	60/week/patient	-
Tab doxy 100 mg	8 per tab	-	56/week/patient
Clindamycin gel 1%	98.5 per gel	197/patient	197/patient

INR: Indian rupee, OPD: Outpatient department

Statistical Methods

Sample size calculation

In this clinical study, same size was calculated from prevalence rate[15] using the formula 4 pq/d^2, with precision error around 5%. With 10% loss to follow-up, a total of 30 per group subjects were recruited leading to a total recruited sample size of 60 subjects.

Statistical Tests

Descriptive statistics included mean and standard deviation for demographic characteristics, ACER, and ICER. Mann–Whitney (non-parametric) test was used for comparison of the number of symptom-free days (acne clear skin) in doxycycline and azithromycin study groups (level of significance $P < 0.001$).

RESULTS

A total of 65 subjects were screened and 60 who met the inclusion and exclusion criteria were randomized into the study. Figure 1 depicts the flow of study subjects. All the subjects ($n = 60$) completed the 8 weeks study period. None withdrew from the study and none required any rescue medication.

ACER

The ACER of doxycycline is 2.8 times more than the azithromycin group, but subjects on azithromycin had 2.7 times more symptom-free days (decreased acne lesion count) when compared to doxycycline group [Table 2].

ICER[5]

The ICER from the patient's perspective was obtained; it was negative (Rs-18.019), as shown in Table 3. The differences in the mean costs (patient's perspective) and the number of symptom-free days in the doxycycline group in comparison with azithromycin group when plotted on the cost-effectiveness plane fell in the fourth quadrant are as shown in Figure 2.

Symptom-free Days in Both Study Groups

The mean number of symptom-free days was 85 days and 31 days in the azithromycin group and the doxycycline

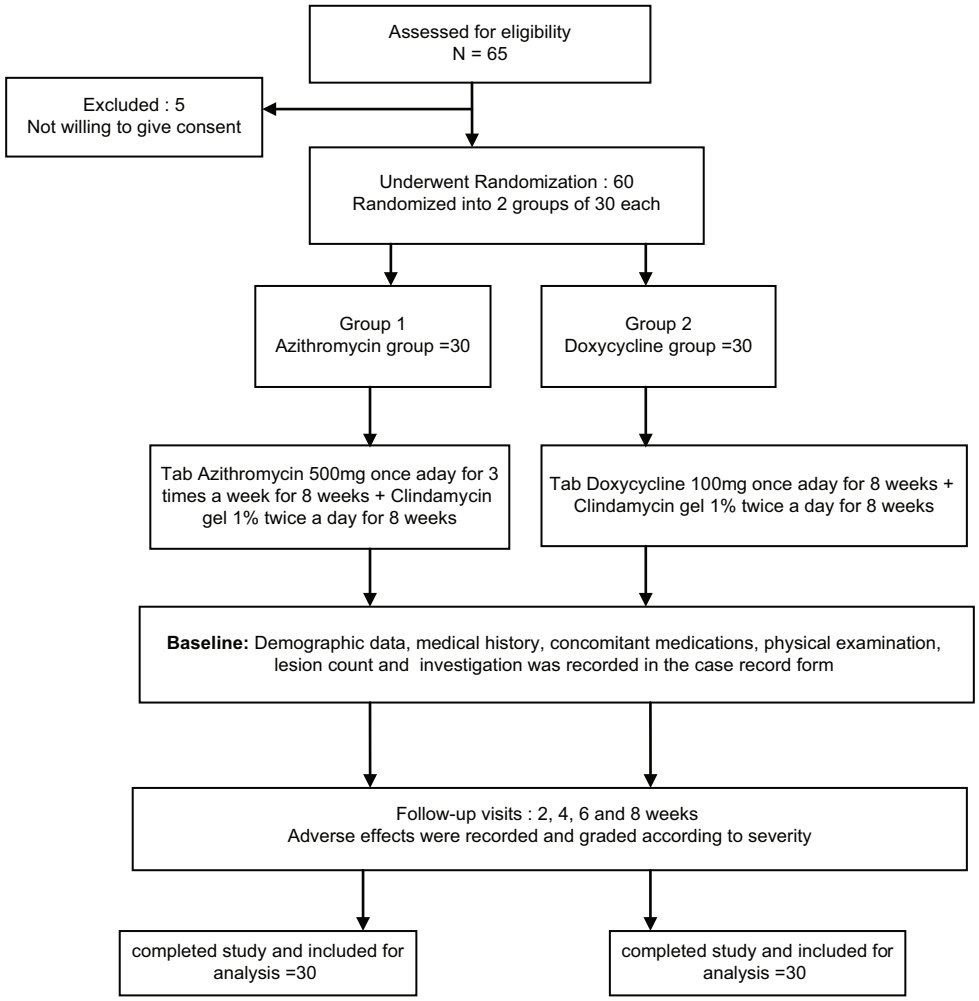

Figure 1: Study flowchart

Table 2: Average cost-effectiveness ratio of doxycycline and azithromycin group

Parameters	Doxycycline+ clindamycin	Azithromycin+ clindamycin
Mean patient perspective cost in INR	Rs. 43419	Rs. 42446
Mean symptom-free days (decrease in acne lesion count)	31 days	85 days
ACER in INR	43419/31	42446/85
ACER (patient perspective)* in INR	1400	499

*Per symptom-free day, ACER: Average cost-effectiveness ratio, INR: Indian rupee

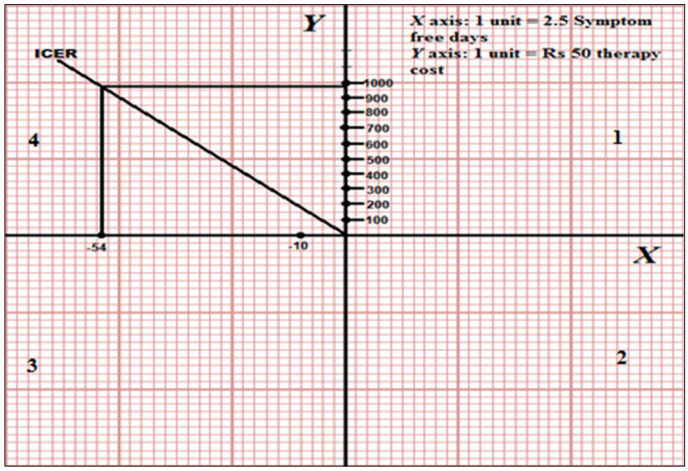

Figure 2: Cost-effectiveness plane of doxycycline in comparison with azithromycin

group, respectively. Mann–Whitney test showed a significant difference both the groups in symptom-free days (U = 288.5 *P* = 0.0087). The 95% confidence interval for the azithromycin group and doxycycline group was 5.941–0.272 and 0.392–2.459, respectively [Figure 3].

Adverse Drug Events

All the adverse events were reported to the pharmacovigilance unit of the institution. There were no serious adverse events reported during the study period. The reported adverse events were mild and self-limiting in nature and did not warrant discontinuation from the study. Three subjects in azithromycin and two subjects in doxycycline group complained of gastritis at 2nd week and 4th week, which was unrelated to study drug.

DISCUSSION

The majority of the study subjects belonged to the age group of 18–25 years with a mean age of study subjects being 22.88 ± 4.13 years. Among the total 60 subjects, (*n* = 34) 56% were male and (*n* = 36) 43% female and among (*n* = 54) 90% subjects were from urban population. The majority of the study subjects (*n* = 41, 68.3%) belonged to the upper-middle

Table 3: Incremental cost-effectiveness ratio of azithromycin and doxycycline

Treatment groups	Mean costs (patient perspective in INR)	Symptom-free days	ICER
Doxycycline	43,419	31	
Azithromycin	42,446	85	
Difference	973	−54	−18.019*

*Negative value of ICER is −18.019 indicates dominance of standard group over the study group. ICER: Incremental cost-effectiveness ratio, INR: Indian rupee

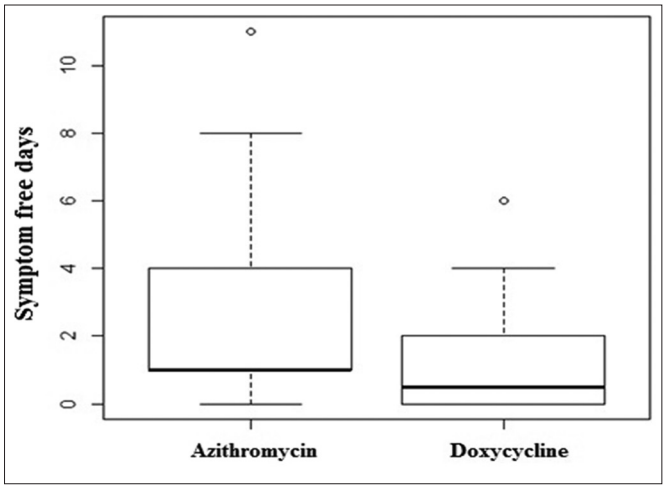

Figure 3: Box plot: Comparison of symptom-free days in azithromycin and doxycycline study groups. Mann–Whitney test, (U = 288.5 P = 0.0087 P is significant)

socioeconomic status. The cost difference between doxycycline and azithromycin group in the management of acne vulgaris was marginal. ACER from the patient's perspective, the mean number of symptom-free days in the azithromycin group was 85 days and that of doxycycline group was 31 days. The cost incurred for a symptom-free day in the doxycycline group was Rs. 1400 and that of azithromycin group was Rs. 499. ICER ratio was obtained by the plotting differences of the mean costs and the number of the lesion from the patient's perspective showed the cost-effectiveness plane in the top left quadrant (fourth quadrant); hence, azithromycin is less expensive. All adverse events reported from the azithromycin (*n* = 3) and doxycycline (*n* = 8) groups were mild, self-limiting, and did not require any intervention.

The average age of study subjects was 22.96 ± 4.11 (mean ± standard deviation [SD]) for azithromycin and 22.96 ± 4.374 (mean ± SD) for doxycycline groups, respectively, the prevalence decreases with increasing age which is consistent with other studies.[16] This also suggests that age is a risk factor in the occurrence of acne vulgaris. Among study subjects, 57% were male and 43% were female could be due to reason that female subjects prefer to attend private clinic than tertiary hospital outpatient department, similar findings seen in the previous study.[17] Among total subjects, 54% of them belonged to urban areas probably due to a sedentary lifestyle,

fatty food intake, and cosmetic purpose. About 68% of the subjects belonged to the upper socioeconomic group which probably reflects the socioeconomic strata of the subjects visiting the tertiary care teaching hospital which points toward an increasing trend to avail quality health-care facilities which were similar to results seen in other study.[18] ACER [Table 2] showed that azithromycin group had relatively lesser cost and more symptom-free days [Figure 3] when compared to doxycycline; hence, azithromycin was more effective. ICER [Figure 2] showed that in this study doxycycline (new intervention), which is compared with azithromycin (standard intervention) falls in the fourth quadrant, indicates that the standard intervention dominates the new intervention with lesser costs and higher effectiveness. The present study therefore indicates that the azithromycin (standard) group with lesser costs and higher effectiveness dominated over the doxycycline (new intervention) group with higher costs and less effectiveness [Figure 2]. The costs and the brands of the study medications remained the same throughout the study period and hence no discounting was necessary. There are no studies comparing the cost effectiveness of this combination of antimicrobials for our comparison.

Strength

This a first of a kind study comparing the cost effectiveness of two oral with topical antimicrobial drugs in the treatment of acne vulgaris; hence, this study aims to help in evaluating cost effectiveness of drugs and the need for the same in the treatment of acne vulgaris.

Limitation

This was an open-labeled exploratory study conducted on a small sample size and in a single center. Follow-up was not done after 8 weeks, which would have shown the rate of recurrence of lesions seen among two groups. Long-term follow-up and multicenter study can help extrapolate the findings of this study.

CONCLUSION

Both the study drugs caused decreased acne lesion count. Both ACER and ICER indicate that an azithromycin is a cost-effective option over doxycycline in the patients' perspectives in the management of acne vulgaris. Doxycycline was relatively less effective and more expensive than the azithromycin group.

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