ORIGINAL RESEARCH

A Randomized Controlled Study of Topical Benzoyl Peroxide with Oral Doxycycline Versus Topical Benzoyl Peroxide with Oral Lymecycline in Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, which has a variable course with acute or insidious onset, relapses, and recurrences. It is one of the most common diseases of patients attending the dermatology clinic. Tetracyclines are the most common oral antibiotic prescribed for acne vulgaris.
Aims: Our study aims to compare the efficacy of topical 2.5% benzoyl peroxide gel (BPO) with oral doxycycline versus topical 2.5% benzoyl peroxide gel with oral lymecycline in the treatment of acne vulgaris.
Methods: The study included 100 patients with acne vulgaris divided into two groups of 50 each. Group A was treated with topical 2.5% benzoyl peroxide gel once daily application at night and capsule doxycycline 100mg twice a day and Group B was treated with topical 2.5% benzoyl peroxide gel once daily application at night and capsule lymecycline 408 mg once a day for 12 weeks. The primary assessment was done using Indian Association of Acne (IAA) grading at baseline and then every fortnight for 12 weeks. Patients were followed up for another 12 weeks after completion of the study.
Results: The grade wise distribution of acne based on IAA grading between the two groups was compared. Chi square test and p-value for all 3 grades of acne at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, and 12 weeks showed statistical improvement among patients in group B at 2, 8 and 10 weeks with p-values of 0.01,0.01 and 0.007, respectively.
Conclusions: From our study it is evident that lymecycline is superior to doxycycline, with much statistical significance among moderate to severe acne.

INTRODUCTION

Acne is a very common and unique disease of human beings.[1] Acne involves the inflammation of the pilosebaceous unit with varied manifestations including comedones, pustules, papules, cysts, nodules, and scarring. [2]

Tetracyclines are the most common oral antibiotic prescribed for acne vulgaris in patients above 12 years. They are classified as first generation (tetracycline, chlortetracycline, oxytetracycline, and demeclocycline), second generation (doxycycline, lymecycline, meclocycline, methacycline, minocycline, and rolitetracycline) third generation (tigecycline),

and fourth generation (azatetracycline, and alkylaminotetracycline. [3, 4]

Doxycycline, a semi synthetic tetracycline is used in the dose of 100 mg BD for 6-12 weeks. Major side effects are phototoxicity, nausea, vomiting, diarrhea, and abdominal pain.

Lymecycline, a Lysinomethyl-tetracycline, water soluble prodrug of tetracycline is approximately 5000 times more soluble than tetracycline and is used in dose of 408mg once daily. It inhibits bacterial ribosomal protein synthesis, has anti-inflammatory & anti-collagenolytic effects, inhibits polymorphonuclear cells and eosinophil chemotaxis, matrix metalloproteinases and pro-inflammatory cytokines: TNF-α, IL-1 & IL-6.[5] The major side effects include discoloration of teeth and enamel hypoplasia, delayed bone growth, diarrhea, and nausea and rarely photosensitivity.[6]

Topical benzoyl peroxide is used in acne to reduce resistance and to aid in the anti-bacterial effect of oral antibiotics. [7, 8] Our study aims to compare the efficacy of topical 2.5% Benzoyl peroxide gel (BPO) with oral Doxycycline versus topical 2.5% Benzoyl peroxide gel with oral Lymecycline in the treatment of acne vulgaris.

METHODS

This is a randomized controlled open labeled prospective interventional study conducted over a period of one year from August 2017 to July 2018 at the outpatient Department of Dermatology at a tertiary center after obtaining Institutional Ethical Committee approval. A total of 100 patients of either sex in age group 14-35 years with clinical diagnosis of acne vulgaris including hormonal acne and drug induced acne were included in the study after obtaining written informed consent. Patients who were on topical or systemic anti acne medications in the last 1month, females yet to complete their family, pregnant and lactating females, patients with known hypersensitivity to any of the components of the study medication, history of regional enteritis/ulcerative colitis/antibiotic associated colitis, severe hepatic, renal or photosensitive disease were excluded from the study. Those patients who developed severe side effects/intolerance during the treatment, who wanted to discontinue the treatment or if they used any other topical medicated creams, lotions, powders, or solutions other than study medication during the study period were also excluded from the study.

During the initial visit, the demographic details such as name, age, sex, marital status, occupation were noted for all the patients in a preformed proforma. History was taken regarding the following details: Presenting complaints, the duration of lesions, associated symptoms, any prior treatment history, intake of drugs that can induce acne, treatment for any hormonal disorders, precipitating factors such as sun exposure, premenstrual flare, stress, smoking, sweating, diet, any significant past or personal history, menstrual & obstetric history in females and family history of acne.

A thorough clinical examination was done in good lighting. Skin type was assessed: oily, dry, or normal type. Numbers, morphological types, and distribution of lesions were all noted down in the proforma. We have taken standard photographs at a constant distance and lighting from three angles: right, left, and straight view of face. It was done at baseline and every 2 weeks till the lesions subsided. General examinations including mucocutaneous sites and systemic

examinations were done in all patients. Features of hirsutism, if any, were noted.

Basic Laboratory investigations such as complete hemogram, liver function test, renal function test, thyroid profile, urine routine and blood sugar values were done in all cases to rule out comorbidities. Patients with Polycystic Ovarian Disease (PCOD) as an etiological factor were screened in the department of Obstetrics and Gynecology and appropriate treatment was instituted.

Patients were allocated into two groups of 50 each, Group A and Group B by simple random sampling. 50 patients in Group A were treated with topical 2.5% Benzoyl peroxide gel once daily application at night and capsule Doxycycline 100mg twice a day for 12 weeks. 50 patients in Group B were treated with topical 2.5% Benzoyl Peroxide gel once daily application at night and capsule Lymecycline 408mg once a day for 12 weeks. Patients were asked to use non-comedogenic sunscreen and to avoid high calorie diet and anabolic steroids.

They were informed about the side effects such as photosensitivity, nausea, vomiting, epigastric pain, diarrhea and burning or stinging sensation following gel application. They were asked to report immediately to us if any.

The primary assessment parameters were done using Indian Association of Acne (IAA) grading at baseline and then every fortnight till 12 weeks or till the lesion subsided. The secondary efficacy parameters used were Physician global assessment score and Patient global assessment score at 4 weeks. Patients were followed up for another 12 weeks after completion of the study.

IAA Grading

IAA grading is based on lesion counting and morphology.

Grade 1 – mild acne: Comedones <30, papules <10, no scarring
Grade 2 – moderate acne: Comedones any number, papules >10, nodules <3 scarring +/-
Grade 3 – severe acne: Comedones any number, papules any number, nodules/cyst >3, scarring +

Physician Global Assessment Score:

Score	Definition	Description
0	Clear	Residual hyperpigmentation and erythema may be present
1	Almost clear	Few scattered comedones and papules
2	Mild	Easily recognizable; less than half of face
3	Moderate	Many comedones, papules, pustules. 1 nodule may be present. More than half of face
4	Severe	Covered with comedones, numerous papules and pustules; few nodules and cysts may or may not be present. Entire face is involved.

Physician global assessment is based on a 5-point scale. It was calculated at baseline and 4 weeks. As per US FDA a score of clear or almost clear or 2-point scale reduction in acne from the baseline is considered a satisfactory improvement.

Patient global assessment score was calculated on a 4-point scale at 4 weeks

among both the groups. The scoring used was:

1 - Much better
2 - Slightly better
3- Same
4 - Worse.

The observations were analyzed using SPSS (version 17). The difference in reduction of severity of lesions at initial visit and follow up was analyzed using Chi – Square test. ($p < 0.05$ is the cut off value for statistical significance).

RESULTS

Out of 100 patients enrolled in our study, only 91 completed their study and 9 patients (5 from group A and 4 from group B) were lost to follow up and hence excluded from the study analysis.

The predominant age in both groups was below 20 years. There was no significant difference between the age distribution in both the groups. In group A, 31 (62%) were female and 19 (38%) were male. In group B, 24(48%) were female and 26 (52%) were male patients.

28 patients in group A and 27 patients in group B were symptomatic. In both the groups pain was the predominant symptom. 4 patients had PCOD in group A and 5 in group B. 5 patients in group A and 8 in group B had drug induced acne.

In group A, 36 patients had comedones, 38 patients had papules, and 11 patients had pustules, cysts and nodules. Among group B, 36 patients had comedones, 38 patients had papules, 22 patients had pustules, 17 patients had cysts and 15 had nodules.

The grade wise distribution of acne based upon IAA grading among both the groups were compared. Chi square test and p values for all 3 grades of acne at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, and 12 weeks showed statistical improvement among patients in group B at 2, 8 and 10 weeks with p values of 0.01,0.01 and 0.007 respectively. (**Table 1**)

With respect to the physician global assessment score, at 4 weeks, among 45 patients of group A, 10 patients had almost clear, 9 patients had clear, 15 patients had mild, and 11 patients had moderate resolution of lesions. Among 46 patients of Group B at 4 weeks, 11 patients had almost clear, 20 patients had clear, 4 patients had mild, and 11 patients had moderate resolution of lesions. The comparative result was statistically significant at 4^{th} week $p= 0.04$ ($p <0.05$) (**Figure 1**).

Comparing the Patients Global Assessment score at 4 weeks, among 45 patients of group A, 11 patients gave much better response, 15 patients gave slightly better response, 19 patients didn't find any improvement. Among 46 patients of group B, 19 patients gave much better response, 16 patients gave slightly better response, 11 patients didn't find any improvement. In both the groups no one experienced a worse response. The result was statistically significant $p= 0.03$ ($p <0.05$) (**Figure 2**).

During follow up relapse of acne was seen in 17.7% of patients in group A and 10.8% in group B. They were treated with topical benzoyl peroxide alone. In group A, 1 patient had epigastric pain, 4 patients developed hyperpigmentation, 3 patients had photosensitivity, among which 2 developed burning sensation following benzoyl peroxide application and among group B, 2 patients had hyperpigmentation, 1 patient had

Table 1. Indian Association of Acne (IAA) grade wise comparison

IAA	Baseline				2 Weeks			
	GROUP A		GROUP B		GROUP A		GROUP B	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Grade 1	15	30	5	10	16	32	4	8
Grade 2	14	28	17	34	14	28	15	30
Grade 3	21	42	28	56	10	20	12	24
Cleared					5	10	15	30
Chi sq	5.78				12.53			
p	0.06				**0.01**			
IAA	4 Weeks				6 Weeks			
	GROUP A		GROUP B		GROUP A		GROUP B	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Grade 1	13	26	8	16	7	14	8	16
Grade 2	10	20	15	30	10	20	3	6
Grade 3	1	2	1	2				
Cleared	16	32	7	14	7	14	13	26
Chi sq	8.51				5.64			
p-value	0.07				0.13			
IAA	8 Weeks				10 Weeks		12 Weeks	
	GROUP A		GROUP B		GROUP A		GROUP B	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Grade 1	8	16			4	8	1	2
Grade 2	1	2						
Grade 3								
Cleared	8	16	11	22	5	10	3	6
Chi sq	9.97				9.89		4.17	
p-value	**0.01**				**0.007**		0.1	

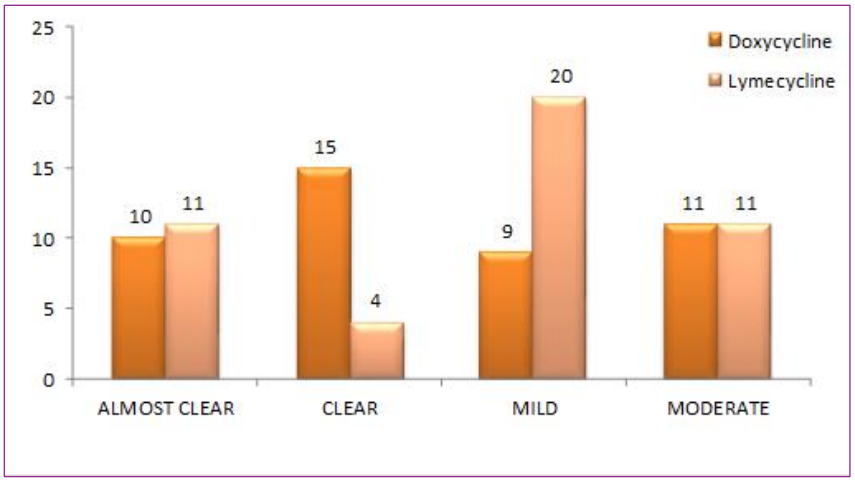

Figure 1. Physician Global Assessment Score.

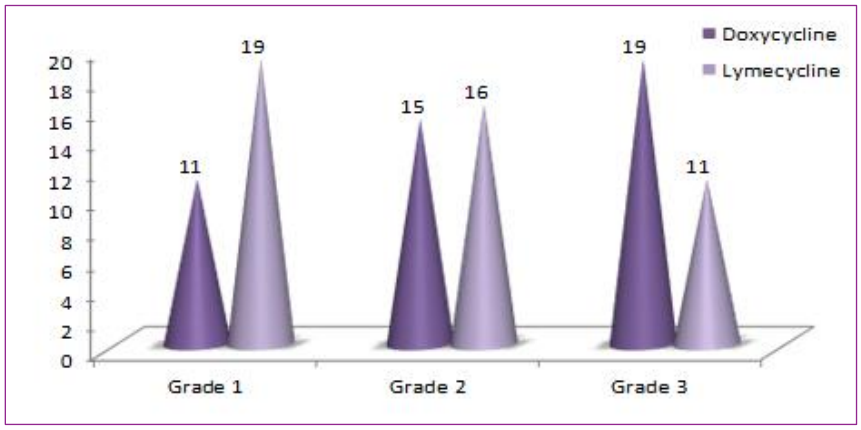

Figure 2. Patient Global Assessment Score.

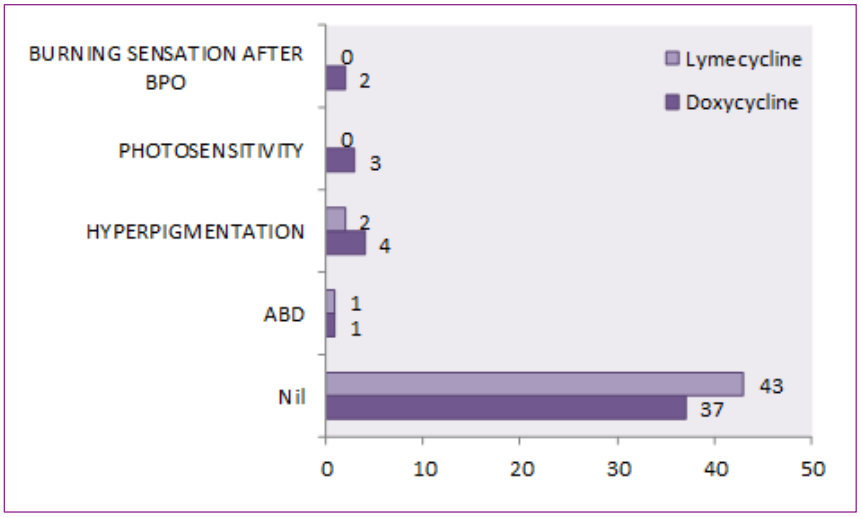

Figure 3. Adverse effects.

diarrhea which settled after probiotic supplementation (**Figure 3**).

DISCUSSION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit and has a variable course with acute or insidious onset, relapses, and recurrences. There are many studies comparing various tetracyclines in the treatment of acne, but hardly any studies that compare lymecycline with doxycycline from. This is one such study wherein we have compared the efficacy of one of the commonly used tetracyclines, doxycycline with the newer lymecycline.

The demographic details obtained from our study from both the groups of totally 100 patients were compared and were found to be similar. In our study the predominant age group was <20 years with 56% in both the groups. Among the patients enrolled in our study females were predominant with 55% and males were 45%. Symptomatic acne with itching, pain or both was 55%.

9% of the patients (4% in group A and 5% in group B) had associated PCOD and underwent hormonal therapy for the same. 10% had drug induced acneiform eruptions. 32% of the patients had a positive family history of acne among siblings and parents. The major morphological pattern of lesion was papules followed by comedones, pustules, nodules, and cyst.

Based upon IAA grading significant statistical improvement was seen among patients in group B (lymecycline group) at 2, 8 and 10 weeks with the reduction in both the number and severity of acne ($p < 0.05$). In group B patients there was a rapid initiation of improvement among the severe grades of acne (grade 3 & 4) (**Figure 4**), where it proved to give results within 8 weeks whereas it took longer time of about 12 weeks in group A. In the less severe grades (grade 1 & 2), both drugs showed similar efficacy. Hence lymecycline can be considered as a first choice of oral antibiotic when treating moderate to severe inflammatory acne.

Papulopustular lesions resolution needed about 8 weeks of Lymecycline therapy, since lymecycline works at all pH and it took 12 weeks with the doxycycline therapy (**Figure 5**). To avoid emergence of antibiotic resistance, monotherapy was avoided and combination with topical 2.5% benzoyl peroxide was given.

This was comparable to a study by Bossyut et al. where among 136 patients, at week 12, the mean percent reduction in inflammatory count was 63% and total lesions counts was 58% for lymecycline. The median percent reduction in non-inflammatory count was 54% for lymecycline. 87% of all patients tolerated the treatments well. Results showed that lymecycline has a comparable efficacy and safety profile.[9]

Lymecycline gave satisfactory results in patients with PCOD associated severe acne in a period of 8 weeks as compared to 12 weeks in Group A. Truncal acne was slower to respond than facial acne which showed response only after at least 8 weeks of treatment.

Among the 45 patients of group A, 22% (10 patients) experienced side effects with 8.8% having hyperpigmentation at their acne site, 6.6% with symptoms of photosensitivity, 2.2% with epigastric pain. 4.4% developed burning sensation after benzoyl peroxide application.

Among the 46 patients of Group B, only 6.5% experienced side effects with 4.5% having

Figure 4. Patient in lymecycline group over 6 weeks.

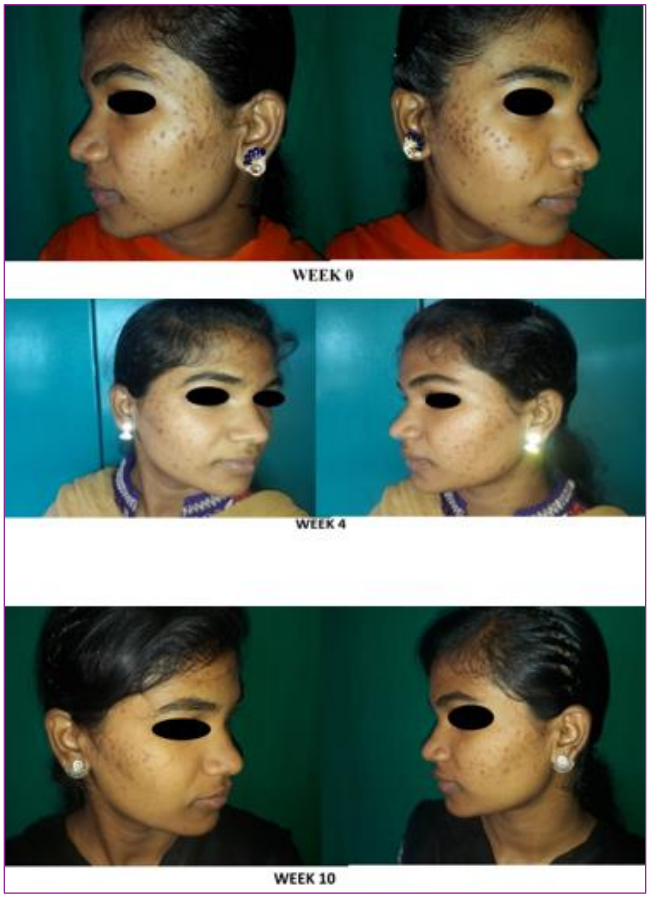

Figure 5. Patient in doxycycline group over 10 weeks.

hyperpigmentation at their acne site, 2.7% had diarrhoea which resolved within a week with probiotics and the drug was continued in that patient. No patient developed symptoms of photosensitivity. Hence it is a drug with very low side effect profile compared to doxycycline.

The side effect profile of lymecycline was much better than that of doxycycline and none of our patients had phototoxic reactions which is one of the added advantages for its use in a tropical country. This was also shown in a study by Bjellerup M et al where it was concluded that doxycycline has a higher phototoxic potency than lymecycline.[10]

CONCLUSION

From our study it is evident that lymecycline is superior to doxycycline, with much statistical significance among moderate to severe acne. There was earlier reduction in lesions and the duration of therapy needed was also less than that needed for doxycycline. But there was not much significant difference in mild forms of acne.

The major advantages of Lymecycline are its once daily dosing which led to improved compliance and better patient satisfaction and the lack of photosensitivity which is advantageous in a tropical country like India.

Conflict of Interest Disclosures: None

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