

COMPARISON OF EFFICACY AND SAFETY OF ISOTRETINOIN VERSUS LYMECYCLINE CAPSULE FOR THE TREATMENT OF ACNE VULGARIS

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Abstract:

Background: Acne vulgaris is a very common condition which can cause significant physical and psychological morbidity. Oral retinoids and tetracyclines have a major role in acne treatment. Isotretinoin (13-cis-retinoic acid) is the only therapy that impacts on all of the major aetiological factors implicated in acne. Another agent is lymecycline, a tetracycline antibiotic have an antibacterial action against P. acnes and also an anti-inflammatory action and used for treatment of acne.

Objectives: To determine the efficacy and safety of Isotretinoin capsules versus Lymecycline capsule in treatment of mild to moderate facial acne vulgaris.

Materials & method: This open labelled, randomized study was conducted in Department of Dermatology and Venereology, Dr. Sirajul Islam Medical College & Hospital Ltd., Dhaka, from December 2021 to May 2022. Patients of mild to moderate facial acne vulgaris were enrolled for study. Clinical examination and relevant investigation were done meticulously. A total number of 50 patients was selected and randomization was done 1:1 parallel design into two groups (group-A and group-B), each of which included 25 patients. Group A patients received Isotretinoin and group B patients were given Lymecycline. Patients were followed up on 2nd, 4th, 8th and finally on 12th week to see clinical improvement and adverse effects. All information was recorded in data collection sheet.

Result: The mean age was found 20.4±5.7 years in group A and 19.9±6.9 years in group B. The mean age difference was not statistically significant ($p>0.05$) between two groups. Male to female ratio was almost 1:3 in the whole study patients. Mean score for open comedone (0.28±0.22 vs. 2.2±1.13), closed comedone (1.92±0.19 vs. 2.08±0.25), papule (0.82±0.29 vs. 1.27±1.04) and pustule (0.85±0.33 vs. 1.19±0.39) was identical in group-A and B respectively and significantly better reduction of acne score ($p=0.001$) in the group A than the group B. It was evident that abdominal discomfort (4.0% vs. 32.0% in group A & B), diarrhea (0% vs. 16.0% in group A & B) and photosensitivity (4.0% vs. 16.0% in group A & B) was predominant in group B. The difference was statistically significant ($p=0.029$). Whereas, erythema and burning was predominant in group A. Mean burning was found 0.15±0.08 in group A and 0.11±0.05 in group B and mean scaling was found 1.27±0.98 in group A and 1.45±0.98 in group B which were statistically non significant ($p>0.05$) between two groups. At 4th follow up mean total safety score was found 3.05±0.92 in group A and 4.65±1.25 in group B.

Conclusion: Isotretinoin was as effective as lymecycline for the treatment of moderately severe acne vulgaris. Both treatments were well tolerated & effective.

Key words: Acne Vulgaris, Isotretinoin, Lymecycline

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Introduction:

Acne vulgaris is global burden of disease. The global number of prevalent cases from 1990 to 2019 increased 156.7 to 231.2 million. The average increase in age-standardized prevalence rates was 0.55% per year¹. Systematic review

reported that family history, age, BMI, dietary factors, smoking and skin type are risk factor of acne².

Acne vulgaris is a chronic inflammatory dermatosis notable for open or closed

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comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules. The pathogenesis is a result of multifaceted processes within the pilosebaceous unit resulting in bacterial overgrowth and inflammation. This condition typically develops at the time of the pubertal transition when changes in the body's hormonal milieu alter pilosebaceous gland function. Factors that can lead to acne are as follow: sebaceous gland produces more sebum, hypercornification of the sebaceous ducts, colonization of *Propionibacterium acnes* in the pilosebaceous ducts and inflammation³.

Current treatments include topical and oral medications that counteract microcomedone formation, sebum production, *P. acnes* and inflammation. These include various topical and oral preparations. First-line treatment for mild acne vulgaris includes benzoyl peroxide or a topical retinoid, or a combination of topical medications consisting of benzoyl peroxide and an antibiotic (erythromycin or clindamycin), retinoid, or both. An alternative treatment would include the addition of a topical retinoid or benzoyl peroxide if not already prescribed; a different retinoid; or topical dapsone (Aczone). First-line treatment for moderate acne vulgaris includes a combination of benzoyl peroxide and a topical antibiotic (erythromycin or clindamycin), topical retinoid, or both³; benzoyl peroxide, an oral antibiotic, and topical retinoid; or benzoyl peroxide, oral and topical antibiotics, and a topical retinoid. Alternative treatments to be considered include a different combination of medications; changing the oral antibiotic; adding a combined oral contraceptive or spironolactone in females; or oral isotretinoin^{4, 5}. Recently study reported that use of Isotretinoin (13-cis-retinoic acid), a non-aromatic retinoid, for acne treatment appears to demonstrate favorable efficacy and safety with low adverse event rates⁶. Oral isotretinoin (ISO) has proven to be a major pharmacological breakthrough for treating severe and recalcitrant cases of inflammatory acne.

Selection of topical therapy is based on severity and type of acne. Topical retinoids, benzoyl peroxide, azelaic acid are effective for mild acne.

Topical antibiotics like clindamycin and erythromycin in which have bacteriostatic, and anti-inflammatory properties are effective in mild to moderate acne²⁻⁴. Antibiotic resistance in acne is a concern. Oral isotretinoin (ISO), which may be used for more severe cases, affects multiple acnegenic pathways. Clinical studies and global experience have shown that ISO provides complete or nearly complete remission of acne, with sustained therapeutic benefit after completion of ISO therapy found to be a consistent observation in the vast majority of treated patient⁶⁻⁹.

Another drug for acne treatment is Lymecycline. Lymecycline is a broad-spectrum tetracycline antibiotic, have an antibacterial action against *P. acnes* and also an antiinflammatory action and are used for inflammatory acne (papules/pustules). *Propionibacterium acnes* is the main bacteria that is stopped by lymecycline. This bacteria feeds on sebum produced by sebaceous glands on the skin. The waste product produced by the bacteria is what causes the glands to become irritated and inflamed. Mitigating this process stops the formation of spots¹⁰. Comparative study between isotretinoin and lymecycline therapy reported that both treatments reduced clinical acne grades and the abundance of *Propionibacterium*¹¹.

Rationale of this study is to find out the effectiveness of drugs in treatment of acne. A lot of patients, mainly young and adolescent patients regularly attended in hospital for treatment of acne vulgaris. Acne leads to significant morbidity that is associated with residual scarring and psychological disturbances such as poor self-image, depression, and anxiety, which leads to a negative impact on quality of life. A myriad of treatment choices is available to treat patients with acne. Treatment options should be tailored to the individual patient with considerations for the patient's preferences, tolerability and safety of the agent. Although effectiveness of other drugs for acne were studied previously, till the effectiveness of isotretinoin and lymecycline therapy not evaluated. Therefore aim of this study was to evaluate the efficacy, safety and

patients' satisfaction of lymecycline and isotretinoin in the treatment of acne vulgaris.

Several other similar studies have been described the treatment and treatment outcome of acne. Zaenglein et al (2016) reported that systemic therapy is recommended in the management of moderate and severe acne. The tetracycline class of antibiotics should be considered first-line therapy in moderate to severe acne. Retinoid are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions⁹. Comparative study between isotretinoin and lymecycline therapy reported that both treatments reduced clinical acne grades and the abundance of Propionibacterium¹¹. Thiboutot et al (2018) demonstrated that new and improved treatments are continuously being developed, and the role of various agents is changing. In the era of antimicrobial resistance, there should be diminished use of antibiotics. Because of their preventive action in acne by targeting microcomedones, isotretinoids should form the cornerstone of acne treatment⁸.

Methodology:

This open labelled, randomized study was conducted in Department of Dermatology and Venereology, Dr. Sirajul Islam Medical College & Hospital Ltd., Dhaka, to compare the efficacy and safety of Isotretinoin capsules and Lymecycline capsule in the treatment of Acne Vulgaris. Study period was December 2021 to May 2022. Patients of mild to moderate facial acne vulgaris were enrolled for study. Clinical examination and relevant investigation were done meticulously. However, the patients were selected after fulfilling the following inclusion and exclusion criteria:

Inclusion criteria:

- Patients of mild to moderate facial acne vulgaris

Exclusion criteria:

- Subjects with acne conglobata, acne fulminans (secondary acne) or other dermatological conditions
- Pregnant and lactating women
- Females on oral contraceptives
- History of hypersensitivity to drugs
- Use of any topical anti acne drugs in past 14 days.

Sample size: The sample size was determined by the following formula

$$n = \frac{Z^2 \times (p) \times (1 - p)}{c^2}$$

where,

n = the sample size for infinite population

z = 1.96 (the value of z distribution, at 95% confidence interval)

p = Proportion in the population. Epidemiological study in Bangladesh reported that 41.6% were moderate, 16.7% were severe and 12.5% were very severe according to GAGS. So prevalence of moderate to severe acne considered as 71%¹⁴.

q = 1 - p, or 0.29.

c = confidence interval, expressed as decimal (which is assumed to 10% or 0.1)

Therefore, n=79. According to time and resource availability 50 samples were collected. After fulfilling the inclusion and exclusion criteria, finally 50 patients were selected and randomization was done 1:1 parallel design into two groups (group-A and group-B), each of which included 25 patients. Group A was received Isotretinoin and group B patients given Lymecycline. Patients was followed up on 2nd, 4th, 8th and finally on 12th week to see clinical improvement and adverse effects.

Complete history, general, physical and dermatological examinations was done for all enrolled patients. History and physical findings was recorded in a structured questionnaire. Group A patients given capsules Isotretinoin started at a dose of 0.5 mg/kg daily and group B was given lymecycline 408 mg once daily in the morning. In addition, use of the gentle skin cleanser at least prior to applying the study medication, and moisturizing lotion in the morning for symptomatic relief of skin dryness, irritation was encouraged. A sun-protection factor (SPF) 50 sunscreen also advised and recommended for used in case of outdoor activities. Patients was followed up on 2nd, 4th, 8th and finally on 12th week to see clinical improvement and adverse effects. Patients are advised to wash face with suitable cleanser and dry it well. Efficacy parameters were: number of non inflammatory lesions (open and closed comedones), number of inflammatory lesions (papules, pustules) and number of total lesions. Lesions count was done on face at screening, baseline and during treatment and at the end of

12 weeks. Clinical response was assessed by percentage reduction of lesion count performed by dermatologist. The safety of the instituted treatment modalities were analyzed on the basis of the results of assessments of incidence and severity of the symptoms of adverse effects (erythema, burning, pruritus, scaling and dryness) graded and recorded by the investigator at different follow up time using Investigator’s Global Assessment (IGA) of acne severity scale (0 = none to 4 = severe). Efficacy of these treatment modalities was assessed from the obtained improvements of each parameter at the agreed times of assessment. All information was recorded in data collection sheet. Statistical analysis of the data was done using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) software version 22. Qualitative data was compared using Chi-square test and quantitative data by independent t-test. $P < 0.05$ was taken as statistically significant.

Ethical consideration: Prior to commencing of the study, permission was taken from authority of Department of Dermatology and Venereology and informed written consent was taken from each patients after explanation of study aim, objective, risk & benefits.

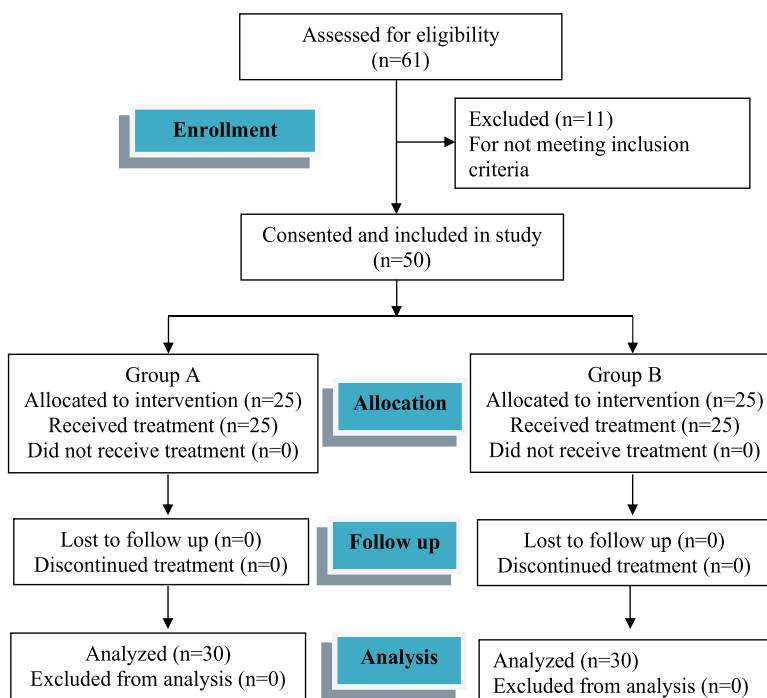
Operational definition:

Acne vulgaris: Acne vulgaris typically affects those areas of the body that have the greatest

number of sebaceous glands, including the face, neck, chest, upper back, and upper arms. In addition to the typical lesions of acne vulgaris (eg, open comedones, closed comedones, and inflammatory lesions), scarring and postinflammatory hyperpigmentation can occur, which can be greatly distressing for some patients. Hyperpigmentation is most common in patients with darker complexions, and an individual lesion may take several months or more to resolve without treatment.

Classification: There is no universal classification system for acne vulgaris; the extensive variety of clinical presentations would make it challenging to develop and implement such a system. A description of the actual lesions encountered was most useful when considering management of acne. Patients may have primarily comedonal acne consisting of noninflammatory lesions (closed and/or open comedones), primarily inflammatory acne with papules, pustules, and/or nodules, or a variable mixture of both. In inflammatory acne, lesions that are less than 5 mm in diameter are generally considered papules and pustules; nodular lesions are greater than 5 mm. Nodular acne is sometimes inaccurately referred to as “cystic” or “nodulocystic” acne. In reality, true cysts are rare. The presence of scarring or postinflammatory hyperpigmentation is also assessed.

Consort flow chart:



Result & Observation:

It was observed that majority (44.0%) patients were age belonged to 16-20 years in group A and 9(36.0%) patients were age belonged to ≤15 years in group B. The mean age was found 20.4±5.7 years in group A and 19.9±6.9 years in group B. The mean age difference was not statistically significant (p>0.05) between two groups. Socioeconomically middle class (42.0%) comprising the major percentage of the patients (Figure I). At 2nd follow up mean acne score of open comedones was found 2.15±0.36 in group A and 5.73±1.3 in group B. At 3rd follow up mean acne score of open comedones was found 1.88±0.28 in group A and 2.85±1.4 in group B. At 4th follow up mean acne score of open comedones was found 0.28±0.22 in group A and 2.2±1.13 in group B which were statistically significant (p<0.05) between two groups (Table II).

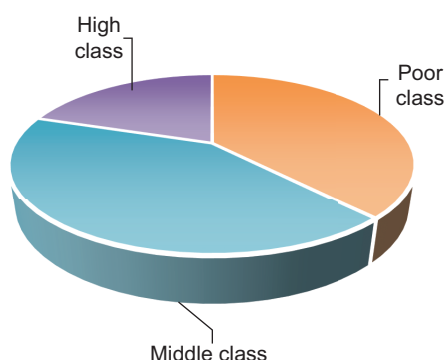


Figure- I: Socioeconomic status of the study population (n=50)

Figure II shows the acne score of close comedones in different follow up. At 2nd follow

up mean acne score of closed comedones was found 5.91±1.06 in group A and 7.4±1.57 in group B. At 3rd follow up mean acne score of closed comedones was found 3.27±0.98 in group A and 4.03±1.07 in group B. At 4th follow up mean acne score of closed comedones was found 1.92±0.19 in group A and 2.08±0.25 in group B which were statistically significant (p<0.05) between two groups. Table III shows acne score of papule in different follow up. At 2nd follow up mean acne score of papules was found 3.92±1.47 in group A and 4.94±1.63 in group B. At 3rd follow up mean acne score of papules was found 2.67±0.92 in group A and 3.8±1.12 in group B. At 4th follow up mean acne score of papules was found 0.82±0.29 in group A and 1.27±1.04 in group B which were statistically significant (p<0.05) between two groups.

Table IV shows acne score of pustule in different follow up. At 2nd follow up mean acne score of pustules was found 2.09±1.09 in group A and 4.92±1.3 in group B. At 3rd follow up mean acne score of pustules was found 1.04±0.5 in group A and 1.83±1.05 in group B. At 4th follow up mean acne score of pustules was found 0.85±0.33 in group A and 1.19±0.39 in group B which were statistically significant (p<0.05) between two groups. Figure-3 shows total acne score in different follow up. At 2nd follow up mean of total acne score was found 14.07±1.81 in group A and 20.99±1.86 in group B. At 3rd follow up mean of total acne score was found 8.86±0.97 in group A and 12.51±0.8 in group B. At 4th follow up mean of total acne score was found 3.87±0.69 in group A and 6.74±0.53 in group B. Percent reduction of acne severity from base line to final follow up was 90.3±3.38 in group A and 83.5±3.51 in group

Table-I
Distribution of the study patients by age & sex (n=50)

Variables	Group A(n=25)		Group B(n=25)		P-value
	n	%	n	%	
Age					
≤15	5	20.0	9	36.0	
16-20	11	44.0	6	24.0	
21-25	5	20.0	4	16.0	
26-30	2	8.0	5	20.0	
>30	2	8.0	1	4.0	
Mean±SD	20.4	±5.7	19.9	±6.9	0.781 ^{ns}
Range (min-max)	13	-33	12	-37	
Sex					
Male	6	24.0	5	20.0	
Female	19	76.0	20	80.0	

B which were statistically significant ($p < 0.05$) between two groups.

Figure-4 shows the evaluation of safety score in different follow up. At 1st follow up mean total safety score was found 12.16 ± 1.09 in group A and 14.06 ± 1.27 in group B. At 2nd follow up mean total safety score was found 8.78 ± 0.87 in

group A and 10.61 ± 1.02 in group B. At 3rd follow up mean total safety score was found 5.04 ± 1.05 in group A and 7.11 ± 1.4 in group B. At 4th follow up mean total safety score was found 3.05 ± 0.92 in group A and 4.65 ± 1.25 in group B which were statistically significant ($p < 0.05$) between two groups.

Table-II

Acne score of open comedones in different follow up (n=50)

Open comedones	Group A(n=25)		Group B(n=25)		P value
	Mean	±SD	Mean	±SD	
Baseline	12.32	±1.25	12.46	±1.34	0.704 ^{ns}
1 st follow up	9.84	±1.65	9.63	±1.27	0.616 ^{ns}
2 nd follow up	2.15	±0.36	5.73	±1.30	0.001 ^s
3 rd follow up	1.88	±0.28	2.85	±1.40	0.001 ^s
4 th follow up	0.28	±0.22	2.20	±1.13	0.001 ^s

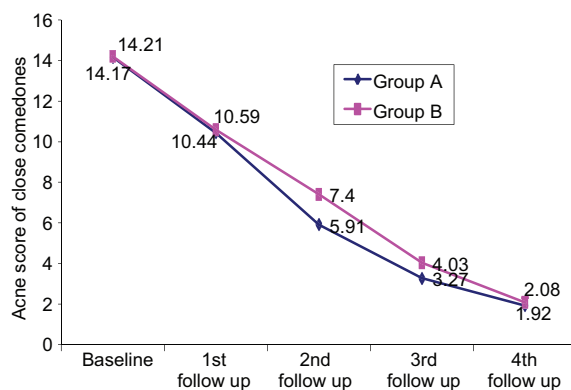


Figure-2: *Acne score of close comedones in different follow up (n=50)*

Table-III

Acne score of papule in different follow up (n=50)

Papule	Group A(n=25)		Group B(n=25)		P value
	Mean	±SD	Mean	±SD	
Baseline	9.60	±2.18	9.71	±2.61	0.872 ^{ns}
1 st follow up	6.12	±1.69	6.80	±1.73	0.166 ^{ns}
2 nd follow up	3.92	±1.47	4.94	±1.63	0.024 ^s
3 rd follow up	2.67	±0.92	3.80	±1.12	0.001 ^s
4 th follow up	0.82	±0.29	1.27	±1.04	0.042 ^s

Table-IV

Acne score of pustule in different follow up (n=50)

Pustule	Group A(n=25)		Group B(n=25)		P value
	Mean	±SD	Mean	±SD	
Baseline	4.01	±2.44	4.45	±2.40	0.523 ^{ns}
1 st follow up	3.18	±1.88	3.54	±1.92	0.506 ^{ns}
2 nd follow up	2.09	±1.09	2.92	±1.30	0.018 ^s
3 rd follow up	1.04	±0.50	1.83	±1.05	0.001 ^s
4 th follow up	0.85	±0.33	1.19	±0.39	0.001 ^s

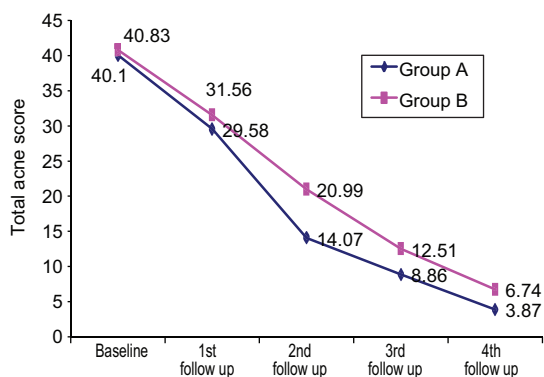


Figure-3: Total acne score in different follow up (n=50)

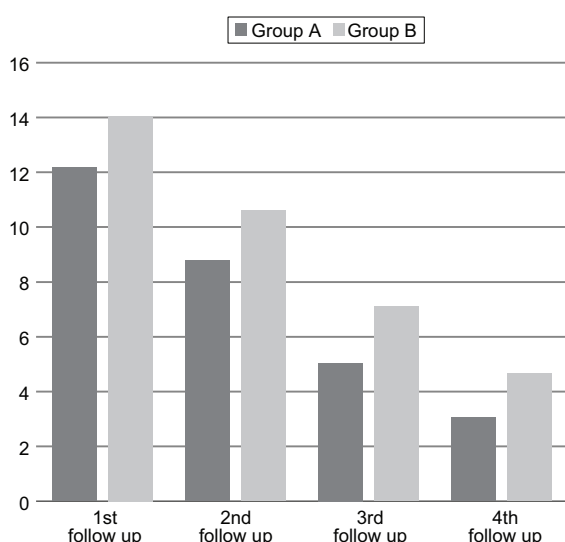


Figure-4: Evaluation of safety score in different follow up (n=50)

Discussion:

In this study a total of 50 patients of mild to moderate facial acne vulgaris were included. It was observed that mean age was found 20.4±5.7 years varied from 13 – 33 years in group A and 19.9±6.9 years varied from 12 – 37 years in group B. The mean age difference was not statistically significant (p>0.05) between two groups. Findings consistent with result of study of previous trial. Previous study noted that approximately 83–100% of all adolescents experience acne vulgaris at some point of their lives^{12, 13}. Acne is one of the most common disorders treated by dermatologists and other health care providers. While it most often affects adolescents, it is not uncommon in adults and can also be seen in children¹³.

In this study mean score for open comedone, closed comedone, papule and pustule was identical between two groups at base line (p>0.05). Significantly better reduction of acne score for open comedone, closed comedone, papule, pustule and total acne score was noticed better at 2nd and 3rd follow up (p<0.005) in the group A than the group B. At 4th follow up mean of total acne score was found 3.87±0.69 in group A and 6.74±0.53 in group B. Percent reduction of acne severity from base line to final follow up was 90.3±3.38 in group A and 83.50 ± 3.51 in group B. Percent reduction of acne severity was significant (P<0.05) more in group A.

Recently study reported that use of Isotretinoin (13-cis-retinoic acid), a non-aromatic retinoid, for acne treatment appears to demonstrate favorable efficacy and safety with low adverse event rates⁶. Oral isotretinoin (ISO) has proven to be a major pharmacological breakthrough for treating severe and recalcitrant cases of inflammatory acne.

Comparative study between isotretinoin and lymecycline therapy reported that both treatments reduced clinical acne grades and the abundance of Propionibacterium¹¹. Lymecycline is a broad-spectrum tetracycline antibiotic, have an antibacterial action. But Antibiotic resistance in acne is a concern. Clinical studies and global experience have shown that isotretinoin (ISO) provides complete or nearly complete remission of acne, with sustained therapeutic benefit after completion of isotretinoin therapy found to be a consistent observation in the vast majority of treated patient⁶⁻⁹. Together, these results indicate that isotretinoin may be a potential option for topical treatment of acne vulgaris.

Conclusions:

Present study concluded that Isotretinoin was as effective as lymecycline for the treatment of moderately severe acne vulgaris. Both treatments were well tolerated & effective.

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